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(54) 2-Oxoethyl derivatives as immunosuppressants

2-Oxoethylderivate als Immunosuppressiva

Dérivés de 2-oxoéthyle comme agents immunosuppresseurs

R2 . R3 incorrect

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(56) References cited:
EP-A- 0 038 758 WO-A-92/00278

- J.MED.CHEM. vol. 35, no. 23, 13 November 1992, USA pages 4284 - 4296 J.R.HAUSKE ET AL. 'DESIGN AND SYNTHESIS OF NOVEL FKBP INHIBITORS'
- IL FARMACO ED.SC. vol. 43, no. 12, 1988, pages 989 - 1003 R.CIABATTI ET AL. 'PROLYL DERIVATIVES OF ENALAPRIL AS POTENTIOAL ANGIOTENSIN CONVERTING ENZYME INHIBITORS'

Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

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D scription

Background

The invention relates to compounds for controlling inflammatory processes in humans through mediation of inflammatory cell proliferation. More particularly, the present invention relates to a class of novel compounds which bind to the FKBP-type family of immunophilins and which are useful for suppressing T-lymphocytes.

EP - 0 038 758 discloses amino acid derivatives which inhibit enkephalinase and have analgesic and hypotensive activity.

In IL Farmaco, Ed. Sc., Vol. 43 (12), pp. 989-1003, R. Ciabatti and coworkers describe the synthesis of prolyl derivatives of enalapril as potential angiotensin converting enzyme inhibitors. However, the tested compounds showed no in vivo activity and only a weak in vitro inhibitory activity.

Compounds which retard the production of cytokines such as interleukin-2 (IL-2) are known. For instance, U.S. Patent No. 4,764,503 assigned to Sandoz Ltd., Basel, Switzerland, describes a compound generically referred to as Cyclosporin A (hereinafter referred to as "CsA"), and U.S. Patent No. 4,894,366 assigned to Fujisawa Pharmaceuticals, Osaka, Japan, describes a compound they designate as "FK506". Both CsA and FK 506 are claimed to inhibit IL-2 production and bind to cellular receptor proteins that possess Peptidyl Prolyl Isomerase (PPIase) activity (Johansson et al., 1990, Trans-plantation 50:10017).

It was initially postulated by those skilled in the art that the specific binding by such compounds to PPIase type proteins led to inhibition of the protein's isomerase activity which, in turn, led to inhibition of T-cell proliferation. Thus, these PPIase type proteins were referred to as "immunophilins", with the cellular receptor proteins that bound to CsA and FK506 being referred to as "cyclophilin" and "FK506 binding protein", respectively. FK506 binding protein is also simply referred to as "FKBP" (Harding et al., 1989, Nature 341:758).

Recent publications report that the inhibition of PPIase activity, in and of itself, is not sufficient for immunosuppressant activity. However, there is support in the literature that inhibitory binding to PPIase-type enzymes probably contributes to ultimate T-cell suppression (Sigal et al. 1991, J. Exp. Med. 173:619).

This disclosure presents a new class of synthetic compounds that both suppress the proliferation of T-cells and inhibit the isomerase activity of the FKBP-type of PPIases.

CsA, a cyclic undecapeptide, has received FDA approval for use as an adjunct to organ transplant procedures. However, CsA is administered with caution due to its known toxicity. Currently, CsA is prescribed in situations where the risks of non treatment outweigh the risks of its therapeutic complications.

As a result, efforts to expand the application of CsA into non life threatening indications such as chronic maintenance of autoimmune disorders have been limited by the well-known side effects of this drug. The use of CsA leads to a variety of disorders including: nephrotoxicity, such as impairment of glomerular filtration and irreversible interstitial fibrosis (Kopp et al., 1991, J. Am. Soc. Nephrol. 1:162); neurological deficits, such as involuntary tremors, or non-specific cerebral angina such as non-localized headaches (De Groen et al, 1987, N. Engl. J. Med. 317:861); and vascular hypertension with complications resulting therefrom (Kahan et al., 1989, N. Engl. J. Med. 321:1725).

Recent efforts to investigate the cause of the adverse effects of CsA administration have centered on the role of CsA breakdown into toxic metabolites (Bowers et al., 1990, Clin. Chem. 36:1875; Burke et al., 1990, Transplantation 50:901). The prevailing thought is that CsA toxicity is due to such metabolites and not due to the nature of the CsA binding to the PPIase, cyclophilin (Akagi et al., 1991, J. Int. Med. Res. 19:1; Ryffel et al., 1988, Transplantation 46:905).

Thus, inhibitor compounds that do not resemble CsA structurally, yet bind to PPIases, should be more amenable to therapeutic applications. Such non-toxic immunosuppressors would benefit the art, especially for chronic administration such as required in the treatment of autoimmune disorders.

The compound FK506 is structurally different from CsA and does not produce the same type of toxic metabolites. FK506 has been shown to be effective in some transplant patients who do not respond to CsA (Tucci et al., 1989, J. Immunol. 143:718).

However, testing of FK506 in humans was delayed due to severe vasculitis observed in treatment regimens in dogs and baboons (Collier et al., 1988, Transplant Proc. 20:226). Furthermore, other clinical side effects and complications of FK506 administration are being reported (Frayha et al., 1991, Lancet 337:296; Kitahara et al., 1991, Lancet 337:1234). It has also been reported that "overall, the absolute rate of clinical rejection in FK506 [post-organ transplantation] patients is only slightly lower than with current standard therapies" (Holechek, 1991, Anna. J. 18:199).

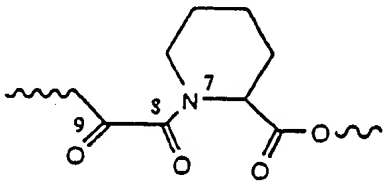
In an attempt to alleviate the FK506 side effects, many minor modifications to the base structure have been reported. For example, U.S. Patent No. 5,057,608 assigned to Merck & Co. and WIPO Publication No. WO89/05304 assigned to FISONS PLC Inc. both disclos chemical variations of the FK506 compound.

To date only a few studies on the metabolism of FK506 have been published, and little information has been reported on th toxicity of its metabolit s (Johansson et al., 1990, Transplantation 50:1001; Christians et al., 1991, Clinical Bio-chemistry 24:271; Lhoest et al., 1991, Pharmaceutica Acta Helvetica 66:302). Since it is likely that the

pattern of metabolism of the FK506 analogs and derivatives are similar to th parent compound, it is also likely that many of th side effects of FK506 will be shared by the derivatives.

As is true for CsA, the toxicity of FK506 is postulated to be based on its structure and not due to its binding activity with the immunophilin FKBP. It is further postulated that the toxicity of compounds such as CsA and FK506 are due to various chemical groups found in these structures which do not participate in the immunosuppressive activity, such as those groups which result in the toxic metabolites of CsA bio-processing. Thus, relatively compact molecules which do not resemble either CsA or FK506, and which have both immuno-suppressive and PPIase binding activity should be free of side effects associated with CsA and FK506.

Furthermore, the compound FK506 and its derivatives (for example such as disclosed in WIPO Publication No. WO92/00278 assigned to VERTEX Pharmaceuticals Inc.) all share the following homo-proline (6-membered, proline-like) dicarbonyl backbone stucture:



FK506 and its derivatives all preferably rely on the two carbonyl groups at positions 8 and 9, with the presence of the carbonyl at the number 8 carbon being essential. The presence of the double bond oxygen in proximity to number 7 nitrogen creates an amide type linkage between the nitrogen at position 7 and carbon at position 8.

Recent reports have suggested that the nitrogen at position 7, along with the number 8 and 9 carbonyl groups of FK506 represent "a twist-bond amide" (Michnick et al., 1991, Science 252:836). Based on the data presented in the Michnick et al. article, it was assumed and accepted by those skilled in this art that the carbonyl at position 8 was the functional species. Jorgensen, 1991, Science 254:954, teaches that this keto-amide moiety is critical to activity because the moiety allegedly serves as a transition state analog.

The present description proposes that the carbonyl group at the number 8 position is non-essential for T-cell suppression, and the compounds of the present invention do not rely on this carbonyl group.

The present invention presents a novel class of synthetic inhibitor compounds. The novel class includes synthetic 2-oxoethylene derivatives that bind to human FKBP-type PPIases and demonstrate human peripheral T-lymphocyte inhibitory activity. Moreover, the absence of a carbonyl attached directly to the nitrogen in the proline ring (see formula II, below) provides compounds that possess stability to hydrolysis by proteases at the N-terminus of proline.

It is therefore an object of the present invention to provide for compounds and compositions containing such 2-oxoethylene derivatives for suppression of pathological and abnormal human peripheral T-lymphocyte proliferation.

It is also an object of the present invention to provide a novel class of compounds suitable for therapeutic compositions designed to suppress pathological immune responses, such as the hyperimmune response in organ transplantation rejection, the self-destructive autoimmune diseases, and the overproduction and excessive proliferation of immune cells such as in infectious disease states.

More specific objects include provisions for compounds, compositions and methods for treatment and prevention of rejection of transplanted organs or tissues such as kidney, heart, lung, liver, bone marrow, skin grafts, and corneal replacement.

It is a further object to provide compounds, compositions and methods for use in the treatment of autoimmune, degenerative, inflammatory, proliferative and hyperproliferative diseases, such as rheumatoid arthritis, osteoarthritis, other degenerative joint diseases, joint inflammation such as associated with infectious diseases such as suppurative arthritis, and secondary arthritis such as those associated with gout, hemochromatosis, rheumatic fever, Sjörgens syndrome and tuberculosis.

Another object is to provide compounds, compositions and methods for use in the treatment of lupus erythematosus, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type 1 diabetes, uveitis, nephrotic syndrome, and of cutaneous manifestations of immunologically-mediated diseases such as psoriasis, atopic dermatitis, contact dermatitis, eczematous dermatitides, seborrheic dermatitis, lichen planus, pemphigus, bollous pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinophilias, and alopecia areata.

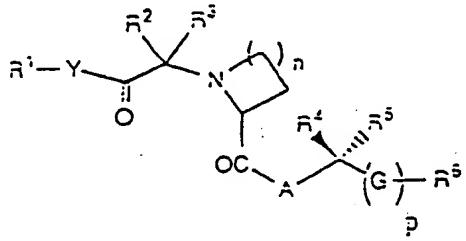
Y t anoth r object is t provide compounds, compositions and methods for use in the tr atment of abnormal T-c ll prolif ration such as lymphocytic leuk mia; Hodgkin's disease, specially thos subtypes involving abnormal T-c ll subpopulations; non-Hodgkin's lymphomas, such as mycosis fungoides, convulated lymphocytic lymphoma, and

immunoblastic sarcoma; and chronic lymphadenitis.

The above lists are non-limiting, and one skilled in the art could easily adapt the compounds, compositions and methods of the present invention to other indications, such adaptations being within the spirit and scope of the invention which will be described her inbelow.

SUMMARY OF THE INVENTION

The presently claimed invention relates to compounds comprising at least one of the following structures:



(I)

wherein

R^1 is

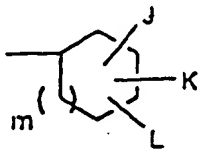
a) hydrogen,
b) linear or branched alkyl (C1-C8) which may be substituted independently or simultaneously up to two times by

i) hydroxy,
ii) phenyl which may be substituted by straight or branched alkyl (C1-C8), or straight or branched alkoxy (C1-C6),
iii) cycloalkyl (C3-C10) which may be substituted by straight or branched alkyl (C1-C8), or straight or branched alkoxy (C1-C6),
iv) bicycloalkyl (C6-C12) which may be substituted by straight or branched alkyl (C1-C10), or straight or branched alkoxy (C1-C6),
v) tricycloalkyl (C7-C14) which may be substituted by straight or branched alkyl (C1-C8), or straight or branched alkoxy (C1-C6),
vi) tetracycloalkyl (C10-C14), which may be substituted by straight or branched alkyl (C1-C8), or straight or branched alkoxy (C1-C6), or
vii) morpholinyl,

c) alkene (C3-C10), diene (C4-C10), or triene (C8-C18), which may be substituted independently or simultaneously, up to three times by

i) phenyl,
ii) straight or branched alkyl(C1-C6), or
iii) straight or branched alkoxy (C1-C6),

d) cycloalkyl (C5-C10), or the cycloalkyl fragment



where

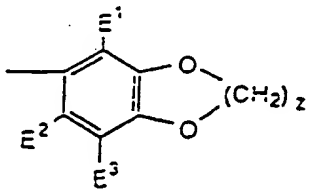
m is an integer of 0, 1, or 2,
J, K, and L are independently or simultaneously

i) hydrogen,
ii) straight or branched alkyl (C1-C5), which may be substituted by phenyl, or straight or branched alkoxy (C1-C6),
iii) straight or branched alkoxy (C1-C5),
iii) phenyl, or
iv) phenyl substituted by straight or branched alkyl (C1-C6), or chlorine, or straight or branched alkoxy (C1-C6),

e) bicycloalkyl (C7-10), tricycloalkyl (C7-14), tetracycloalkyl (C10-C16), or pentacycloalkyl (C11-C20), which may be independently or simultaneously substituted up to 3 times with straight or branched alkyl (C1-C6), or straight or branched alkoxy (C1-C6), or phenyl,
f) the aryl derivatives tetrahydronaphthyl, benzothienyl, benzofuryl, benzopyranyl, furyl, pyridyl, pyranyl, 1,3-oxazolyl, or naphthyl, said aryl derivatives may be independently or simultaneously substituted up to two times by

i) straight or branched alkyl (C1-C6),
ii) straight or branched alkoxy (C1-C6),
iii) halogen, where halogen is fluoro, chloro, bromo, or iodo,

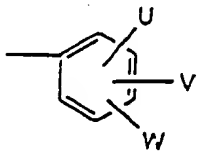
g) the piperonyl fragment



where

z is an integer of 1, or 2,
and E^1, E^2, and E^3 can independently or simultaneously be hydrogen, straight or branched alkyl (C1-C6), straight or branched alkoxy (C1-C6), or chlorine, or

h) the aryl derivative

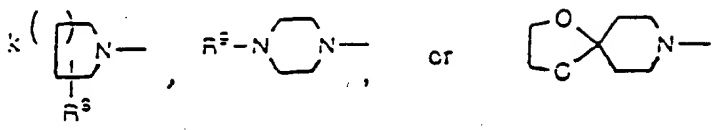


where
U, V, and W can be independently or simultaneously

i) hydrogen,
ii) straight or branched alkyl (C1-C6), straight r branched alkoxy (C1-C6), phenyl, or phenoxy, thes groups may b substituted by phenyl, straight or branched alkoxy (C1-C6), or phenoxy,
iii) hydroxy,

iv) halogen,
v) nitro, or
vi) benzoyl;

Y is a covalent bond, oxygen, NR^7, where R^7 is hydrogen, in addition, R^1-Y- may also be



where

k is an integer of 1 or 2,

R^8 is

a) hydrogen,
b) carboalkoxy with a straight or branched alkoxy (C1-C6),
c) straight or branched alkyl (C1-C6) which may be substituted by phenyl, or straight or branched alkoxy (C1-C6),
d) phenyl, or phenyl substituted by halogen,

R^9 is phenyl which may be substituted by straight or branched alkyl (C1-C6);
R^2 and R^3 are defined as follows: one of R^2 and R^3 are hydrogen, and the other is hydrogen or straight or branched alkyl (C1-C6);
n is an integer of 2 or 3;
A is NR^{10}, where R^{10} is hydrogen or straight or branched alkyl (C1-C6);
R^4 and R^5 may independently or simultaneously be

a) hydrogen,
b) straight or branched alkyl (C1-C8) which may be substituted by

i) phenyl, or phenyl substituted by hydroxy or alkoxy (C1-C2),
ii) cycloalkyl (C5-C6),
iii) alkylthio (C1-C6),
iv) carboxamido,
v) straight or branched alkoxy (C1-C6) which may be substituted by phenyl,

c) phenyl, or
d) cycloalkyl (C3-C7), which may be substituted by straight or branched alkyl (C1-C6),

in addition, R^4 and R^5, taken together can be

$$-(CH_2)_r-$$

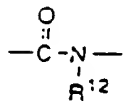
where

r is an integer of 4 or 5;

G is one of the following fragments

$$-HC{=}CH-,\ -CH_2{\cdot}CH_2-,\ \text{or}\ -CH_2-$$

or the following fragment



where R^{12} is hydrogen or methyl, such that the carbonyl group is attached to the carbon bearing R^4 and R^5 and that NR^{12} is connected to R^6;

p is an integer of 0 or 1;

R^6 is

a) hydrogen,
b) straight or branched alkyl (C1-C6) which may be substituted by

i) phenyl,
ii) phenyl substituted with straight or branched alkyl (C1-C6), straight or branched alkoxy (C1-C6), or
iii) pyridyl, or

c) phenyl, naphthyl, furyl, thiofuryl, cycloalkyl (C5-C8), bicycloalkyl (C6-C10), tricycloalkyl (C7-C12), tetracycloalkyl (C10-C16), pentacycloalkyl (C11-C20) or benzoyl, such groups may be substituted by

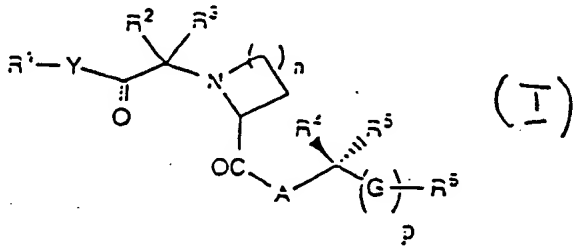
i) an amine,
ii) amino substituted by a straight or branched alkoxycarbonyl (C1-C6) that may be substituted by phenyl or an alkene (C2-C6),
iii) amino substituted by alkanoyl (C1-C6), or benzoyl,
iv) sulfonamide ($-SO_2NH_2$), or
v) hydroxy, or a straight or branched alkoxy (C1-C6), that may be substituted by phenyl;

and pharmaceutically acceptable salts thereof.

Included within the scope of the present invention are pharmaceutically acceptable salts of the above mentioned compounds. Pharmaceutically acceptable salts can be derived from mineral acids, carboxylic acids or sulfuric acids preferred from hydrochloric acid, hydrobromic acid, sulfuric acid, methane sulfuric acid, ethane sulfonic acid, toluene sulfonic acid, benzene sulfonic acid, naphthalene disulfonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, citric acid, fumaric acid, maleic acid or benzoic acid. Most preferred are the hydrochlorides.

In the case of the present compounds being carboxylic acids or containing acidic functional groups, the invention includes metal salts and ammonium salts. Preferred are sodium, potassium or ammonium salts. The compounds of this invention exist as stereoisomeric forms, which either behave like image and mirror image (enantiomers) or not (diastereomers). Included within the scope of the invention are the enantiomers, the racemic form as well as diastereomeric mixtures. Enantiomers as well as diastereomers can be separated by methods known to those skilled in the art (compare E.L. Eliel, Stereochemistry of Carbon Compounds, McGraw Hill, 1962).

Preferred are compounds of formula (I)



(I)

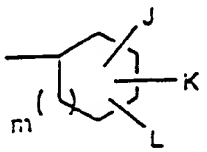
wherein

R^1 is

a) hydrogen,
b) linear or branched alkyl (C1-C6) which may be substituted

i) once by hydroxy,
ii) once by phenyl which may be substituted by straight or branched alkyl (C1-C4), or straight or branched alkoxy (C1-C6),
iii) once by cycloalkyl (C3-C8) which may be substituted by straight or branched alkyl (C1-C6), or straight or branched alkoxy (C1-C4),
iv) once by bicycloalkyl (C6-C10) which may be substituted by straight or branched alkyl (C1-C8), or straight or branched alkoxy (C1-C4),
v) once by tricycloalkyl (C7-C12) which may be substituted by straight or branched alkyl (C1-C6), or straight or branched alkoxy (C1-C4),
vi) once by tetracycloalkyl (C10-C12), which may be substituted by straight or branched alkyl (C1-C8), or straight or branched alkoxy (C1-C4),
vii) up to two times by phenyl and cycloalkyl (C5-C7), or
viii) up to two times by phenyl and morpholinyl,

c) alkene (C3-C8), which may be substituted by phenyl, straight or branched alkyl (C1-C4), or straight or branched alkoxy (C1-C4),
d) diene (C4-C7) substituted by straight or branched alkyl (C1-C6), or straight or branched alkoxy (C1-C4),
e) triene (C10-C16) substituted up to three times by straight or branched alkyl (C1-C6), or straight or branched alkoxy (C1-C4),or
f) cycloalkyl (C5-C10), or the cycloalkyl fragment



where

m is an integer of 0, 1, or 2,
J, K, and L are independently or simultaneously

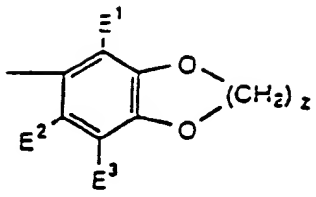
i) hydrogen,
ii) straight or branched alkyl (C1-C5), which may be substituted by phenyl, or straight or branched alkoxy (C1-C4),
iii) phenyl, or
iv) phenyl substituted by straight or branched alkyl (C1-C4), or chlorine, or straight or branched alkoxy (C1-C4),

g) bicycloalkyl (C7-10) which may be substituted up to 3 times with straight or branched alkyl (C1-C6), or straight or branched alkoxy (C1-C4),
h) tricycloalkyl (C7-14) which may be substituted up to 3 times with straight or branched alkyl (C1-C6), or straight or branched alkoxy (C1-C4),
i) tetracycloalkyl (C10-C15) which may be substituted up to 3 times by straight or branched alkyl (C1-C6), or straight or branched alkoxy (C1-C4),
j) naphthyl derivatives, or the heteroaryl derivatives benzothienyl, benzofuryl, benzopyranyl, furyl, pyridyl, pyranyl, or 1,3-oxazolyl, said derivatives may be substituted up to two times by

i) straight or branched alkyl (C1-C6),

ii) halogen,
iii) or both,

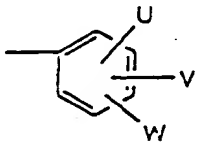
k) 1,2,3,4-tetrahydronaphthyl,
l) the piperonyl fragment



where

z is an integer of 1, or 2,
and E^1, E^2, and E^3 can be independently or simultaneously hydrogen, straight or branched alkyl (C1-C4), straight or branched alkoxy (C1-C4), or chlorine,

m) the aryl derivative

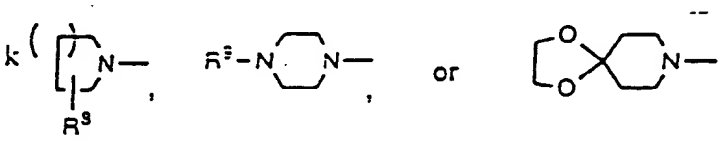


where

U, V, and W can be independently or simultaneously

i) hydrogen,
ii) straight or branched alkyl (C1-C4), which may be substituted by phenyl,
iii) straight or branched alkoxy (C1-C6) which may be substituted by phenyl, straight or branched alkoxy (C1-C4), or phenoxy,
iv) hydroxy,
v) phenyl,
vi) halogen,
vii) nitro,
viii) benzoyl, or
ix) phenoxy;

Y is a covalent bond, oxygen, NR^7, where R^7 is hydrogen,
in addition,
R^1-Y- may also be



wher

k is an integer of 1, or 2,
R^8 is

a) hydrogen,
b) carboalkoxy with a straight or branched alkoxy (C1-C4),
c) straight or branched alkyl (C1-C4) which may be substituted by phenyl, or straight or branched alkoxy (C1-C4), or
d) phenyl, or phenyl substituted by halogen,

R^9 is phenyl which may be substituted by alkyl (C1-C4);

R^2 and R^3 are defined as follows: one of R^2 and R^3 are hydrogen, and the other is hydrogen or straight or branched alkyl (C1-C6);
n is an integer of 2 or 3;
A is NR^{10}, where R^{10} is hydrogen or straight or branched alkyl (C1-C4);
R^4 is

a) hydrogen,
b) straight or branched alkyl (C1-C6) which may be substituted by

i) phenyl, or phenyl substituted by hydroxy or methoxy,
ii) cycloalkyl (C5-C6),
iii) alkylthio (C1-C6),
iv) carboxamido, or
v) straight or branched alkoxy (C1-C6) which may be substituted by phenyl,

c) phenyl, or
d) cycloalkyl (C3-C7), which may be substituted by straight or branched alkyl (C1-C6);

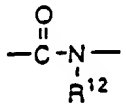
R^5 is hydrogen or straight or branched alkyl (C1-C4), and R^4 and R^5, taken together can be

$$-(CH_2)_r-$$

where r is an integer of 4 or 5;
G is one of the following fragments

$$-HC{=}CH-,\ -CH_2{\cdot}CH_2-,\ \text{or}\ -CH_2-$$

or the following fragment



where the carbonyl group is attached to the carbon bearing R^4 and R^5 and NR^{12}- is connected to R^6,
R^{12} is hydrogen or methyl;
p is an integer of 0 or 1;
R^6 is

a) hydrogen,
b) straight or branched alkyl (C1-C4) which may be substituted by

i) phenyl,
ii) phenyl substituted with straight or branched alkyl (C1-C4), straight or branched alkoxy (C1-C4), or

iii) 2- or 4-pyridyl,

c) phenyl or naphthyl, which may be substituted by

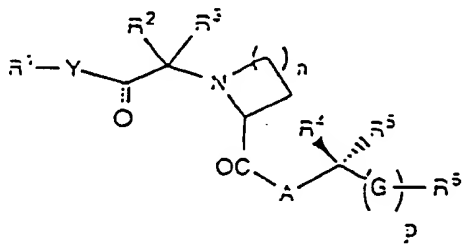
i) amine,
ii) amino substituted by a straight or branched alkoxycarbonyl (C1-C6) that may be substituted by phenyl or an alkene (C2-C6),
iii) amino substituted by alkanoyl (C1-C6), or benzoyl,
iv) sulfonamide ($-SO_2NH_2$), or
v) straight or branched alkoxy (C1-C6), that may be substituted by phenyl,

d) benzoyl,
e) furyl, or thiofuryl, or
f) cycloalkyl (C5-C8), bicycloalkyl (C6-C10), tricycloalkyl (C7-C12), or tetracycloalkyl (C10-C14);

and pharmaceutically acceptable salts thereof.

Included within the scope of the present invention are pharmaceutically acceptable salts of the above mentioned compounds. Pharmaceutically acceptable salts can be derived from mineral acids, carboxylic acids or sulfuric acids preferred from hydrochloric acid, hydrobromic acid, sulfuric acid, methane sulfuric acid, ethane sulfonic acid, toluene sulfonic acid, benzene sulfonic acid, naphthalene disulfonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, citric acid, fumaric acid, maleic acid or benzoic acid. Most preferred are the hydrochlorides

Most preferred are compounds of formula (I)



(I)

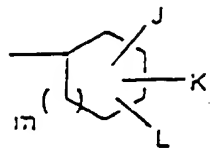
wherein

R^1 is

a) hydrogen,
b) linear or branched alkyl (C1-C6) which may be substituted by

i) hydroxy,
ii) phenyl, or phenyl substituted by straight or branched alkyl (C1-C4),
iii) cycloalkyl (C3-C8) which may be substituted by straight or branched alkyl (C1-C4),
iv) bicycloalkyl (C6-C9) which may be substituted by straight or branched alkyl (C1-C6),
v) tricycloalkyl (C7-C12) which may be substituted by straight or branched alkyl (C1-C4),
vi) tetracycloalkyl (C10-C12), which may be substituted by straight or branched alkyl (C1-C6),
vii) both phenyl and cycloalkyl (C5-C6), or
viii) both phenyl and morpholinyl,

c) alkene (C3-C6), which may be substituted by phenyl,
d) diene (C5-C6) substituted by straight or branched alkyl (C1-C4),
e) triene (C13-C16) substituted up to three times by straight or branched alkyl (C1-C4),
f) cycloalkyl (C5-C6), or the cycloalkyl fragment



where

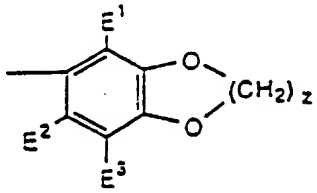
m is an integer of 0, 1, or 2,
J, K, and L are independently or simultaneously

i) hydrogen,
ii) straight or branched alkyl (C1-C5),
iii) phenyl, or
iv) phenyl substituted by straight or branched alkyl (C1-C4), or chlorine, or straight or branched alkoxy (C1-C4),

g) bicycloalkyl (C7-8) which may be substituted up to 3 times with straight or branched alkyl (C1-C4),
h) tricycloalkyl (C7- 12) which may be substituted up to 2 times with straight or branched alkyl (C1-C6),
i) tetracycloalkyl (C10-C12) which may be substituted up to 3 times by straight or branched alkyl (C1-C4),
j) 2-benzothienyl substituted independently or simultaneously at least twice by either

i) straight or branched alkyl (C1-C3),
ii) chlorine,
iii) or both,

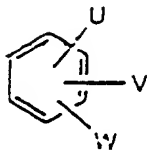
k) 2-furyl,
l) 2-pyridyl,
m) 2-naphthyl,
n) 1,2,3,4-tetrahydronaphthyl,
o) 2-benzopyranyl,
p) 2-benzofuryl,
q) the piperonyl fragment



where

z is an integer of 1, or 2,
and E^1, E^2, and E^3 are hydrogen, or

r) the aryl derivative

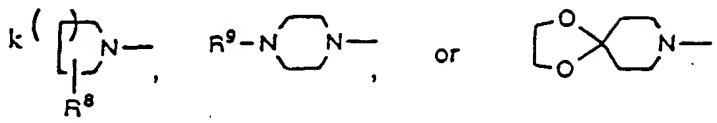


where

U, V, and W can be independently or simultaneously

i) hydrogen,
i) straight or branched alkyl (C1-C4),
ii) straight or branched alkoxy (C1-C4),
iii) alkoxy (C2) substituted by alkoxy (C2), or phenoxy,
iv) hydroxy,
v) phenyl,
vi) fluorine,
vii) chlorine,
viii) bromine,
ix) nitro,
x) benzyloxy,
xi) benzoyl,
xii) phenoxy;

Y is a covalent bond, oxygen, NR^7, where R^7 is hydrogen; in addition, R^1-Y- may also be



where

k is an integer of 1, or 2,
R^8 is

a) hydrogen,
b) carboalkoxy with alkoxy (C1-C2),
c) straight or branched alkyl (C1-C4) which may be substituted by phenyl,
d) phenyl,

R^9 is phenyl;
R^2 and R^3 are defined as follows: one of R^2 and R^3 is hydrogen, and the other is hydrogen or straight or branched alkyl (C1-C4);
n is an integer of 2 or 3:
A is NR^{10}, where R^{10} is hydrogen or methyl;
R^4 is

a) hydrogen,
b) straight or branched alkyl (C1-C4) which may be substituted by

i) phenyl,

ii) cycloalkyl (C5-C6),
iii) alkylthio (C1-C4),
iv) carboxamido, or
v) benzyloxy, or

c) phenyl;

R^5 is hydrogen or straight or branched alkyl (C1-C4), and R^4 and R^5, taken together can be

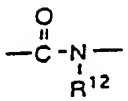
$$-(CH_2)_r-$$

where r is integer 5;

G is one of the following fragments

$$-HC=CH-,\ -CH_2\cdot CH_2-,\ \text{or}\ -CH_2-$$

or the following fragment



where the carbonyl group is attached to the carbon bearing R^4 and R^5 and NR^{12} is connected to R^6,
R^{12} is hydrogen or methyl;
p is an integer of 0 or 1;
R^6 is

a) hydrogen,
b) straight or branched alkyl (C1-C4) which may be substituted by

i) phenyl,
ii) phenyl substituted with alkoxy (C1-C2),
iii) 2- or 4-pyridyl,

c) phenyl which may be substituted by

i) amino,
ii) amino substituted by allyloxycarbonyl,
iii) amino substituted by acetyl,
iv) amino substituted by benzoyl,
v) amino substituted by benzyloxycarbonyl,
iii) sulfonamide ($-SO_2NH_2$), or
iv) straight or branched alkoxy (C1-C4),

d) benzoyl,
e) furyl,
f) naphthyl,
g) cycloalkyl (C5-C8), or
h) tetracycloalkyl (C10-C12);

and pharmaceutically acceptable salts thereof.

Included within the scope of the present invention are pharmaceutically acceptable salts of the above mentioned compounds. Most preferred are the hydrochlorides.

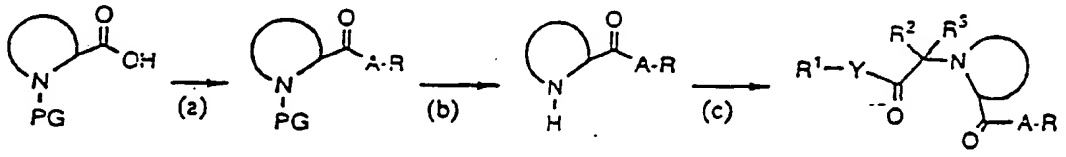
The following examples of compounds according to the invention are particularly preferred:

L-Isoleucine, N-[1(2-Benzyloxy-2-Oxoethyl)-L-Prolyl]Benzylamide;
L-Isoleucine, N-[1-(2-Methoxy-2-Oxoethyl)-L-Prolyl]Benzylamide;
L-Isoleucine, N-[1-(2-Phenyl-2-Oxoethyl)-L-Prolyl]Benzylamide;
L-Isoleucine, N-[1-(2-Naphth-2-yl-2-Oxoethyl)-L-Prolyl]Benzylamide;
L-Isoleucine, N-[1-(2-(Biphenyl-4-yl)-2-Oxoethyl)-L-Prolyl]Benzylamide;
L-Isoleucine, N-[1-(2-(2-Methoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(5-Chloro-3-Methyl-benzo[B]thiophene-2-yl)-2-Oxoethyl)-L-Prolyl]Benzylamide;
L-Isoleucine, N-[1-(2-(trans,trans-Hexa-2,4-dienyl-1-oxy)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(4-Chlorophenyl)-2-Oxoethyl)-L-Prolyl]Benzylamide;
L-Isoleucine, N-[1-(2-(4-Methylphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(4-Methoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-Methyl-N-[1-(2-Phenyl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-Phenyl-2-Oxoethyl)-L-Homoproline] Benzylamide;
L-Phenylglycine, N-[1-(2-Phenyl-2-Oxoethyl)-L-Proline Benzylamide;
L-Isoleucine, N-[1-(1-Methyl-2-Phenyl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(3-Methoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(3,4-Dihydroxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-Methyl-N-[1-(2-Benzyloxy-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(Carbobenzyloxymethylene)-L-Homoproline Benzylamide;
L-Isoleucine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(Carbo-tert-Butoxymethylene)-L-Proline] Benzylamide;
L-Isoleucine, N-[1-(2-tert-Butyl-2-Oxoethyl)-L-Proline] Benzylamide;
L-Isoleucine, N-[1-(2-(2,5-Dimethoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(2,4-Dimethoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(2-Nitrophenyl)-2-Oxoethyl)-L-Propyl] Benzylamide;
L-Isoleucine, N-[1-(2-(4-Nitrophenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(3-Benzyloxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(2,4-Dimethylphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(4-Fluorophenyl)-2-Oxoethyl)-L-Propyl] Benzylamide;
L-Isoleucine, N-[1-(2-(4-Bromophenyl)-2-Oxoethyl)-L-Propyl] Benzylamide;
L-Isoleucine, N-[1-(2,4-Dichlorophenylcarbamoylmethyl)-L-Proline] Benzylamide;
L-Isoleucine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Homoproline] Benzylamide;
L-Isoleucine, N-[1-(2-Furan-2-yl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-Pyrid-2-yl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(Adamant-1-ylcarbamoylmethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(cis-Octahydro-pentalen-1-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-[2-(2,6,6-Trimethyl-Bicyclo[3.1.1]hept-3-yl)-2-Oxoethyl]-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(4-Pentylcyclohexyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(1,2,3,4-tetrahydro-Napththalen-2-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(1-Methyl-Cyclohexyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-Oxo-2-Tricyclo[3.3.1.0 ^{3,7}]Non-3-yl-Ethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-Oxo-3-(3-Methyl-Adamantan-1-yl)-Propyl)-L-Prolyl] Benzylamide;
L-Proline, 1-(2-Adamantan-1-yl-2-Oxoethyl) Benzyl Ester;
L-Isoleucine, N-[1-(2-(Biphenyl-4-yl)-2-Oxoethyl)-L-Prolyl] 1,2,3,4-Tetrahydroisoquinolinamide;
L-Isoleucine, N-[1-(2-(Biphenyl-4-yl)-2-Oxoethyl)-L-Prolyl] Benzyl Ester;
L-Isoleucine, N-[1-(2-(Biphenyl-4-yl)-2-Oxoethyl)-L-Prolyl] tert-Butylamide;
L-Phenylalanine, N-[1-(2-(Biphenyl-4-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Methionine, N-[1-(2-(Biphenyl-4-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
Glycine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Valine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Leucine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Phenylalanine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Norvaline, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Norleucine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Asparagine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-S rine-(O-Benzyl Ether), N-[1(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide;

L-β-Phenylalanine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Cyclohexylalanine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] alpha-(S)-methylbenzylamide;
L-Isoleucine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] alpha-(R)-methylbenzylamide;
L-Isoleucine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Pyridin-4-ylmethylamide;
L-Isoleucine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl]-L-Prolyl] Pyridin-2-ylmethylamide;
L-Isoleucine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] 4-methoxybenzylamide;
L-Isoleucine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] 2-methoxybenzylamide;
L-Isoleucine, N-[1-(Carboxymethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-[2-[N-(Piperidine-3-Carboxylic Acid Ethyl Ester)]-2-Oxoethyl]-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-[2-(N-(4-Benzylpiperidyl))-2-Oxoethyl]-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-[2-(2-Methylpiperidine)-2-Oxoethyl]-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(2-Hydroxyethylamine)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-[2-(4-Phenylpiperazine)-2-Oxoethyl]-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-[2-(1-Pyrrolidine)-2-Oxoethyl]-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-[2-(N-Cyclopentylamino)-2-Oxoethyl]-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-[2-(N-(Phenylmethylamino))-2-Oxoethyl]-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-[2-(N-(Cyclohexylmethylamino))-2-Oxoethyl]-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(4-Phenylpiperidyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-[1-(3,7,11-Trimethyldodeca-2,6,10-trien-1-ol)]-2-Oxoethyl)-L-Proline] Benzylamide;
L-Isoleucine, N-[1-(2-(3-Phenyl-2-Propen-1-Oxy)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(3-Phenyl-3-Methyl-2-Propen-1-Oxy)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(1-Phenylpropoxy)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(1-Phenyl-1-Cyclohexylmethoxy)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(1-Phenyl-2-(4-Morpholino)Ethoxy)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(2-Oxy-2-Methyladamant-2-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(Adamantan-2-ylcarbamoylmethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(Adamant-1-ylmethylcarbamoylmethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(2-Methyl-1-(S)-Phenyl-1-Propoxy)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(2-Methyl-1-(R)-Phenyl-1-Propoxy)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(4-tert-Butylcyclohexyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-Bicyclo[2.2.1]hept-2-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(Chroman-2-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide Hydrochloride Salt;
L-Isoleucine, N-[1-(2-(Benzofuran-2-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide Hydrochloride Salt;
L-Isoleucine, N-[1-(2-(3-Benzoyloxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(4-Benzoyloxaphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(2-Benzoyloxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(3-Phenoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(2-Phenoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(3,4,5-Triethoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(Benzo[1,3]dioxol-5-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-[2-Oxo-2-[4-(2-Phenoxyethoxy)-Phenyl]-Ethyl]-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(4-Phenoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(2,4,6-Trimethoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(2,3-Dimethoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(2,6-Dimethoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(1-(4-Methylphenyl)cyclohexyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(1-(4-Chlorophenyl)cyclohexyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(2,3,4-Trimethoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(1-Phenylcyclohexyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(2,4,5-Trimethoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] L-Proline Benzyl Ester Hydrochloride;
L-Prolin , 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] Benzylamide Hydrochloride;
L-Prolin , 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-Phenethylamide Hydrochloride;
L-Prolin , 1-[2-(3,4,5-Trimethoxyph nyl)-2-Oxoethyl] 3-Phenylpropylamid Hydrochlorid ;
L-Prolin , 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 4-Phenylbutylamide Hydrochloride;

L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-(Pyrid-2-yl)ethylamide Dihydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-3-Oxoethyl] 2-(4-aminophenyl)ethylamide Dihydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 3-(4-[N-Carballyloxy]aminophenyl)propyl Ester Hydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-Phenyl-2-oxoethylamide;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] Tetrahydrofurfurylamide;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] Naphthalen-1-ylmethylamide;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-(4-Sulfamoylphenyl)ethylamide;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 4-Phenylpiperidenylamide;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 4-Methoxybenzamide Hydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 3-Methoxybenzamide Hydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-Methoxybenzamide Hydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] N-Methylphenethylamide Hydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] (S)-α-methylbenzylamide Hydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] (R)-α-methylbenzylamide Hydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 1-methyl-3-phenylpropylamide Hydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] Adamant-1-ylmethylamide Hydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 1-(R)-(1-naphthyl)ethylamide Hydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] Cyclohexylmethylamide;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] Diphenylmethylamide Hydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] tert-Butylamide Hydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 1,2-Diphenylethylamide Hydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] Cyclohexyl amide Hydrochloride;
1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] L-Homoproline Benzyl Ester Hydrochloride;
L-Homoproline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] Benzylamide Hydrochloride;
L-Homoproline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] Adamant-1-ylmethylamide Hydrochloride;
L-Homoproline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] tetrahydrofurfurylamide;
L-Homoproline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-(4-Sulfamoylphenyl)ethylamide;
L-Homoproline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] (S)-α-methylbenzylamide Hydrochloride;
L-Homoproline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] (1-(S)-[2'-(S)-methylpropyl]-3-phenylprop-2-E-enyl)-amide;
L-Homoproline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] (1-(S)-[2'-(S)-methylpropyl]-3-phenylpropyl)-amide;
L-Isoleucine, N-[1-(2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl)-L-Homoprolyl] Benzylamide;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-(4-(N-Acetyl)aminophenyl)ethylamide;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-(4-(N-Benzoyl)aminophenyl)ethylamide;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-(4-(N-carboalloxy)aminophenyl)ethylamide;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-(4-(N-Carbobenzyloxy)aminophenyl)ethylamide;
L-Homoproline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 3-(4-(N-Carboallyloxy)aminophenyl)propyl Ester Hydrochloride;
L-Proline, 1-[2-Adamantan-1-yl-2-Oxoethyl] 3-(4-(N-Carboallyloxy) aminophenyl)propyl Ester Hydrochloride; and
L-Homoproline, 1-[2-Adamant-1-yl-2-Oxoethyl] 3-(4-(N-Carboallyloxy)aminophenyl)propyl Ester Hydrochloride.

According to another aspect the invention also concerns a method for making the compounds of formula (I), comprising the following steps:



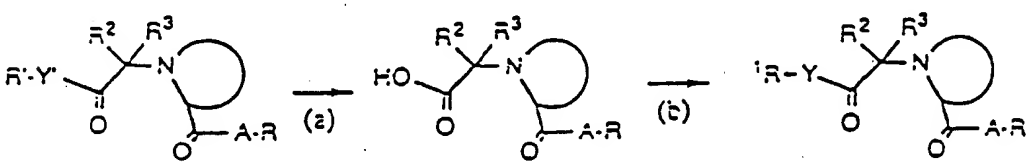
which are

(a) coupling an N-protected imino acid to an amin or an alcohol to form a C-substitut d, N-protected imino acid;

(b) removing the protecting group from said C-substituted, N-projected imino acid; and

(c) alkylating the resulting imino acid from step (b) at the nitrogen position with an α-halo ester, α-halo ketone, or an α-halo amide.

According to another aspect of the invention there is provided another method for making the compounds of formula (I), comprising the following steps:

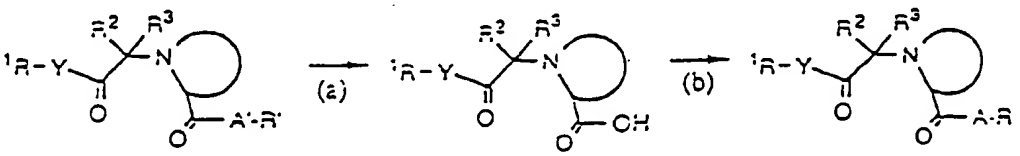


which are

a) deprotecting the 2-position of a first 2-oxoethyl derivative; and

b) coupling the resulting acid derivative from step (a) to form a second 2-oxoethyl derivative.

According to still another aspect of the invention there is provided another method for making the compounds of formula (I) comprising the following steps:

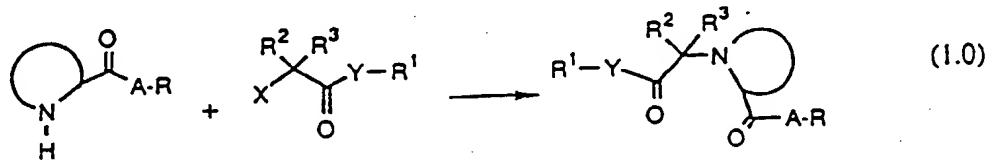


which are

a) deprotecting the imino acid C-termini of a 2-oxoethyl derivative to form a 2-oxoethyl imino acid; and

b) coupling said 2-oxoethyl imino acid resulting from step (a) with an amine or an alcohol to form a C-substituted, 2-oxoethyl imino acid derivative.

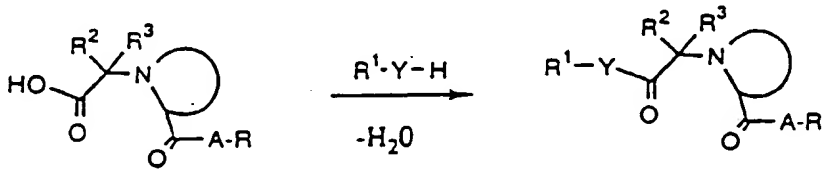
Preferred Method of Synthesis



(I.0)

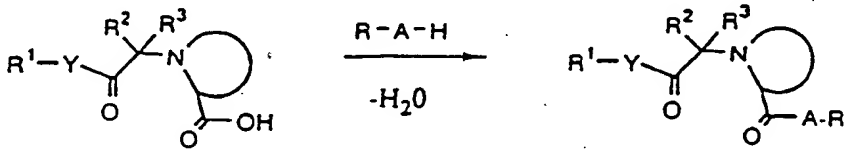
A convenient route to prepare the present compounds was to alkylate selected cyclic imino acids with α-substituted methyl carbonyl compounds (Eq. 1.0). The α-substitution could be in the form of halides such as chloride, bromide and iodide, but can be extended to other groups that are ameanable for displacement. Solvents useful for effecting this transform include ethyl ether, tetrahydrofuran, alcohol solvents, or nitrile solvents such as acetonitrile. In certain cas s, it may be advantageous not to us solvents. There are a number of possible conditions and variations that could b us d for this type of synth sis route, such possibilities being well known to those skilled in the art. (For xampl , se Miyazawa, 1980, T. Bull. Chem. Soc. Japan 53:2555).

When properly substituted, the products from the reaction depicted in Eq. 1.0 can themselves serve as intermediates for the synthesis of other analogs. Hence 2-alkoxy derivatives of these 2-oxoethyl analogs can be converted to the corresponding acid derivatives using methods known in the art (T. W. Greene et al, Protective Groups in Organic Synthesis, 2nd Edition; John Wiley & Sons, 1991). The acid functionality that results may be converted to an activated acyl derivative and coupled to an appropriate Y-R1 derivative using methods described earlier (Bodanszky The Practice of Peptide Synthesis: Springer-Verlag, Vol 21, 1984).



(2.0)

In another embodiment, substituted 2-oxoethyl derivatives may be converted to active embodiments of this invention by coupling to an appropriate A-R derivative using methods described in the literature (Bodanszky The Practice of Peptide Synthesis: Springer-Verlag, Vol 21, 1984).



(3.0)

The alpha-halo ketones and esters used are either commercially available or can be prepared from steps available in current literature. For example, the alpha-halo esters can be prepared from the corresponding alcohols by treatment with alpha-halo acetylhalides such as alpha-chloro acetylchloride, and the alpha-halo ketones can be prepared from the corresponding carboxylic acids. Thus, the carboxy groups are transformed. into either an acid chloride or an anhydride and treated with diazomethane to provide the corresponding alpha-diazo ketone. The diazo ketones are converted to alpha-halo ketones upon treatment with hydrogen halides such as HCl.

The presently claimed compounds were found to be effective at low micromolar doses in both in vitro PPIase enzyme inhibition assays and in vivo assays for inhibition of mitogen-induced human T-cell proliferation. Moreover, the results from the graft vs. host assay (described in detail further below) indicate that the present class of compounds exhibit desirable biological properties (prophylactic prevention of lymph node swelling), with no obvious toxicity at 100 mg/kg concentrations.

The present invention encompasses pharmaceutical formulations which, in addition to non-toxic, inert pharmaceutically suitable excipients, contain the compounds of the invention.

The present invention also includes pharmaceutical formulations in dosage units. This means that the formulations are present in the form of individual part, for example, tablets, dragees, capsules, caplets, pills, suppositories and ampules, the active compound content of which corresponds to a fraction or a multiple of an individual dose. The dosage units can contain, for example, 1, 2, 3 or 4 individual doses; or 1/2, 1/3 or 1/4 of an individual dose. An individual dose preferably contains the amount of active compound which is given in one administration and which usually corresponds to a whole, one half, one third or one quarter of a daily dose.

By non-toxic inert pharmaceutically suitable excipients there are to be understood solid, semi-solid or liquid diluents, fillers and formulation auxiliaries of all types.

Preferred pharmaceutical formulations which may be mentioned are tablets, dragees, capsules, caplets, pills, granules, suppositories, solutions, suspensions and emulsions, paste, ointments, glues, creams, lotions, dusting powders and sprays. Tablets, dragees, capsules, caplets, pills and granules can contain the active compounds in addition to the customary excipients, such as (a) fillers and extenders, for example, starches, lactose, sucrose, glucose, mannitol and silicic acid, (b) binders, for example, carboxymethylcellulose, alginates, gelatin and polyvinylpyrrolidone, (c) humectants, for example, glycerol, (d) disintegrating agents, for example, agar-agar, calcium carbonate and sodium carbonate, (e) solution retarders, for example, paraffin and (f) absorption accelerators, for example, quaternary ammonium compounds, (g) w tting ag nts, for example, cetyl alcohol and glycerol monostearate, (h) absorbents, for xampl , kaolin and bentonite and (i) lubricants, for xample, talc, calcium stearate, magnesium stearate and solid polyethylene glycols, or mixtures of th substances listed under (a) to (i) directly hereinabove.

The tablets, dragees, capsules, caplets, pills and granules can be provided with the customary coatings and shells, optionally containing opacifying agents and can also be of such composition that they r lease the active compounds only or preferentially in a certain part of the intestinal tract, optionally in a delayed manner. Examples of embedding compositions which can be used are polymeric substances and waxes.

The active compounds can also be present in microencapsulated form, if appropriate with one or more of the abovementioned excipients.

Suppositories can contain, in addition to the active compounds, the customary water-soluble or water-insoluble excipients, for example, polyethylene glycols, fats, for example, cacao fat and higher esters (for example, C_{14} -alcohol with C_{16} -fatty acid), or mixtures of these substances.

Ointments, pastes, creams and gels can contain, in addition to the active compounds, the customary excipients, for example, animal and vegetable fats, waxes, paraffins, starch tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures of these substances.

Dusting powders and sprays can contain, in addition to the active compounds, the customary excipients, for example, lactose, talc, silicic acid, aluminum hydroxide, calcium silicate and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, for example, chlorofluorohydrocarbons.

Solutions and emulsions can contain, in addition to the active compounds, customary excipients, such as solvents, solubilizing agents and emulsifiers, for example, water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, glycerol formal, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, or mixtures of these substances.

For parenteral administration, the solutions and emulsions can also be in a sterile form which is isotonic with blood.

Suspensions can contain, in addition to the active compounds, customary excipients, such as liquid diluents, for example, water, ethyl alcohol or propylene glycol and suspending agents, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum methydroxide, bentonite, agar-agar, and tragacanth, or mixtures of these substances.

The abovementioned pharmaceutical formulations can also contain other pharmaceutical active compounds in addition to the claimed compounds of the present invention.

The aforementioned pharmaceutical formulations are prepared in the customary manner by known methods, for example, by mixing the active compound or compounds with the excipient or excipients.

The formulations mentioned can be used either with humans and animals, orally, rectally, bucally, parenterally (intra-venously, intramuscularly or subcutaneously), intracisternally, intravaginally, intraperitoneally or locally (dusting powder, ointment or drops) and for the therapy of infection in hollow spaces or body cavities. Suitable formulations are injection solutions, solutions and suspensions for oral therapy, gels, pour-on formulations, emulsions, ointments or drops. Ophthalmological and dermatological formulations, silver salts and other salts, ear drops, eye ointments, powders or solutions can be used for local therapy.

It is furthermore possible to use gels, powders, dusting powders, tablets, sustained release tablets, premixes, concentrates, granules, pellets, capsules, caplets, aerosols, sprays and inhalates on humans and animals. The compounds according to the invention can furthermore be incorporated into other carrier materials, such as, for example, plastics (e.g., chains of plastic for local therapy), collagen or bone cement.

DETAILED DESCRIPTION

The following describes a preferred way to prepare the compounds of the present invention.

REAGENTS AND INSTRUMENTS:

Anhydrous tetrahydrofuran (THF), ethyl ether (Et_2O), and acetonitrile were distilled from calcium hydride prior to use. Unless otherwise stated, all reagents discussed in the following examples were commercially available from Aldrich Chemical Co, Milwakee, WI, or Janssen Chimica through the U.S. vender Spectrum Chemicals Mfg. Corp., New Brunswick, NJ. The general procedure for converting methyl-ketones to α-bromoketones (unless otherwise specified) was according to steps described in Jaques et al., 1988, Org. Synth. Coll. 6:175-178. --

All reactions were carried out in oven-dried glassware (140 °C) which were cooled under argon prior to use. Crude products were purified by flash column chromatography using 230-400 mesh silica gel (35-70 um) or medium/high pressure liquid chromatography using Shimadzu LC-8A Preparative liquid chromatography system equipped with columns packed with either 20 um or 10 um silica. Thin layer chromatography (TLC) was performed on aluminum-backed silica gel plates, and visualization was accomplished with a UV light or an iodine vapor chamber.

Proton (^1H) nuclear magnetic resonanc (NMR) spectra were obtained on GE-OMEGA-300 spectrom ters at 300 MHz. Carbon (^{13}C) NMR w re obtained on these same spectrometers at 75 MHz. Mass spectral data w re obtained

on a Kratos-MS 80RFA spectrometer using electron impact ionization (EI), chemical ionization (CI), or fast atom bombardment (FAB). Mass Spectral (MS) data were obtained on a Kratos CONCEPT I-H spectrom ter, using liquid-cesium secondary ion (LSI) technique, a more modern version of fast atom bombardment (FAB).

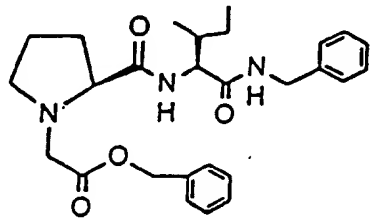
Melting points were obtained on a Thomas Hoover capillary melting point apparatus in open-ended capillaries and are not corrected.

General Process for Preparing alpha-halo Ketones from Carboxylic Acids.

2-Chloro-4'-(n-Pentyl) Acetophenone. A solution of 4-pentyl-benzoic acid (1.178 g, 6.13 mmol) and oxalyl chloride (630 uL, 855 mg, 6.74 mmol, 1.1 eq) in dichloromethane (15 mL) was stirred at 22 °C for 10 min, then treated with one drop of N,N-dimethylformamide at 22 °C {Caution, gas evolution may become brisk}. After gas evolution was no longer observed, the flask was fitted with a condenser and warmed to reflux for 30 min. The solution was cooled to -5 °C, and cannulated into a cold (-5 °C), ethereal solution of diazomethane (40 mL). After the solution was stirred at -5 °C for 30 min, the flask was removed from the cold bath and the yellow solution was allowed to stir at 22 °C for 2 hrs (preferably in the dark). The solution was concentrated in vacuo, and purified by flash chromatography (5% ethyl acetate in hexane) to provide 33 mg (1.3%) of 2-chloro-4'-(n-pentyl) acetophenone and 586 mg (44%) of 4'-(n-pentyl) diazoacetophenone as a bright yellow oil.
Rf (10% ethyl acetate in hexane) = 0.37
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, J = 8.1 Hz, 2 H), 7.20 (d, J = 7.9 Hz, 2 H), 5.93 (s, 1 H, C<u>H</u>N_2), 2.60 (m, 2 H), 1.58 (m, 2 H), 1.27 (m, 4 H), 0.86 (t, J = 6.9 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.78 (C=O), 149.05, 134.92, 129.31, 127.43, 54.47 (C=N_2), 36.53, 32.06, 31.46, 23.14, 14.64.

The diazo compound was quickly taken up in ethyl acetate (120 mL), and the solution was cooled to -5 °C. To this was added a 1.0 M solution of HCl in ether (Aldrich, 6.0 mL). Gas evolution was observed, and the yellow solution became colorless. The flask was removed from the cold bath and the solution was allowed to stir at 22 °C for 2 hrs. The solution was poured into a separatory funnel, washed with satd aq $NaHCO_3$, dried ($MgSO_4$) and concentrated in vacuo to provide 0.595 g (98% based on starting diazo compd.) of 2-chloro-4'-(n-pentyl) acetophenone as a colorless oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 6.5 Hz, 2 H), 7.23 (d, J = 6.5 Hz, 2 H), 4.64 (s, 2 H, C<u>H</u>$_2$Cl), 2.60 (m, 2 H), 1.58 (m, 2 H), 1.28 (m, 4 H), 0.86 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.25 (C=O), 150.55, 132.55, 129.55, 129.27, 46.85 (<u>C</u>H_2Cl), 36.63, 32.06, 31.34, 23.14, 14.65.

Example 1



L-Isoleucine, N-[1-(2-Benzyloxy-2-Oxoethyl)-L-Prolyl] Benzylamide.

a) <u>N-(tert-Butoxycarbonyl)-L-Isoleucine Benzylamide</u>. Into a 500 mL round bottomed flask equipped with a magnetic stirrer was added N-(tert-butoxycarbonyl)-L-isoleucine (22.53 g, 97.39 mmol, 1.0 eq) and THF (300 mL). The solution was stirred until homogeneous, cooled to -5 °C, and treated with N-ethylmorpholine (14.23 mL, 12.88 g, 112.0 mmol, 1.15 eq). The solution was stirred at -5 °C for 20 min and isobutyl chloroformate (13.24 mL, 13.90 g, 102 mmol, 1.05 eq) was added dropwise over 10 min. After stirring at -5 °C for 30 min, benzylamine (12.24 mL, 12.0 g, 112.0 mmol, 1.15 eq) was added dropwise over 10 min. After the addition was complete, the flask was removed from the cold bath and the solution was stirred at 22 °C for 2.5 hrs. The solution was concentrated to a residue, and partitioned between ethyl acetate (200 mL) and water (100 mL). The aqueous layer was extracted with ethyl ether (2 X 100 mL) and discarded. The organic extracts were combined, washed with 1N HCl (5 X 50 mL), 1 N NaOH (3 X 50 mL), satd. aq NaCl (50 mL), and dried ($MgSO_4$). The solution was concentrated in vacuo to provide 29.93 g (96 %) of N-(tert-butoxycarbonyl)-L-isoleucine benzylamide as a white solid.
mp = 125-126 °C
R_f(100% ethyl acetate) = 0.74
R_f (50 % thyl acetat in hexane) = 0.60

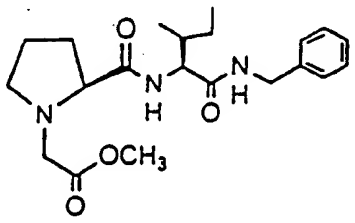
b) L-Isoleucine Benzylamide. Into a 500 mL round bottomed flask equipped with a magnetic stirrer was added N-(tert-butoxycarbonyl)-L-isoleucine benzylamide (29.93 g, 93.53 mmol, 1.0 eq) and dichloromethane (300 mL). The solution was stirred at 22 °C for 10 min until homogeneous, and trifluoroacetic acid (43.22 mL, 63.97 g, 0.57 mol, 6.0 eq) was added (Caution: gas evolution may be brisk!). After TLC analysis indicated that the reaction was complete, the solution was concentrated to an oil, and used directly in the next experiment.

c) N-Carbobenzyloxy-L-Proline-L-Isoleucine Benzylamide. Into a 1-L round bottomed flask equipped with a magnetic stirrer was added N-carbobenzyloxy-L-proline (25.618 g, 102 mmol, 1.0 eq), and dichloromethane (300 mL). The solution was cooled to 0 °C, and oxalyl chloride (10.15 mL, 15.02 g, 118.31 mmol, 1.15 eq) was added. After stirring at 0 °C for 5 min, five drops of N,N-dimethylformamide were added (Caution: gas evolution may be brisk!). The solution was stirred at 0 °C for 5 min, the flask was removed from the cold bath, and the solution was stirred at 22 °C for 9 hrs. The solution was concentrated in vacuo to remove all volatiles, dissolved in fresh dichloromethane (300 mL), and cooled to -5 °C. This solution was cannulated into a cooled (0 °C) solution containing L-isoleucine N-benzylamide and triethylamine (75.71 g, 748 mmol) dissolved in dichloromethane (100 mL). After the addition was complete, the flask was removed from the cold bath, and the solution was stirred at 22 °C for 3 hrs. The solution was poured into a seperatory funnel and washed with water (3 X 75 mL), 1 N HCl (7 X 100 mL), 1 N NaOH (4 X 100 mL), satd. aq NaCl (100 mL), and dried ($MgSO_4$). The solution was concentrated in vacuo to provide a crude residue. The residue was recrystallized (ethyl acetate/hexane) to provide 28.72 g (68%) of the product as a white solid. The mother liquor was concentrated to an oil and purified by flash chromatography (20 % ethyl acetate) to provide 7.88 g (18.6%) of additional product, or 36.60 g (86%) of the title compound as a white solid.
mp = 151-153 °C
R_f (50 % ethyl acetate in hexane) = 0.18
Mass Spectrum (+EI) m/e (rel intensity) 451 (20,M+), 395 (18), 345 (8), 317 (100) 232 (42), 204 (63).

d) L-Proline-L-Isoleucine Benzylamide. A solution of N-carbobenzyloxy-L-proline-L-isoleucine benzylamide (36.60 g, 80.95 mmol), 10% palladium on carbon (0.957 g), and methanol (700 mL) was degassed and purged repeatedly (15 times) with hydrogen, and stirred under an atmosphere of hydrogen at 22 °C. When TLC analysis indicated the reaction was complete, the solution was purged with argon, filtered through a plug of celite, and concentrated in vacuo to provide 23.71 g, (92%) of the title compound as a white solid.
mp = 135-136 °C
R_f(100% ethyl acetate) = 0.08

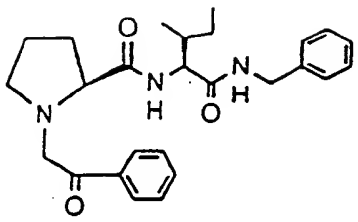
e) L-Isoleucine N-[1-(2-Benzyloxy-2-Oxoethyl)-L-Prolyl] Benzylamide. A solution of L-proline-L-isoleucine benzylamide (10.22 g, 32.20 mmol), and sodium carbonate (6.824 g, 64.39 mmol, 2.0 eq), in acetonitrile (150 mL) was warmed to reflux until homogeneous, cooled to 22 °C, and treated with benzyl 2-bromoacetate (14.75 g, 64.39 mmol, 2.0 eq). The flask was returned to the oil bath and warmed to reflux until TLC indicated the reaction was complete. The heterogeneous solution was filtered, concentrated to a residue, taken up in ethyl acetate (400 mL), and washed with satd aq $NaHCO_3$ (2 X 50 mL). The solution was dried ($MgSO_4$), concentrated to a residue, and purified by flash chromatography (20% ethyl acetate in hexane) to provide 14.80 g (99%) of the title compound as a colorless oil. The ^1H NMR analysis of this compound was consistent with the structure.
R_f (100% ethyl acetate) = 0.63

Example 2



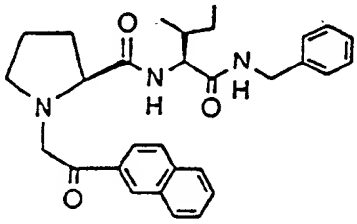
L-Isoleucine, N-[1-(2-Methoxy-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (47 mg, 0.15 mmol), with sodium carbonate (31 mg, 0.29 mmol, 2.0 eq), and m thyl alpha-bromoacetat (113 mg, 0.74 mmol, 5.0 eq) in acetonitril (5 mL), provided 50 mg (87%) of the title compound as a white foam. Th 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
R_f (50% dichlorom thane in thyl acetate) = 0.50

Example 3



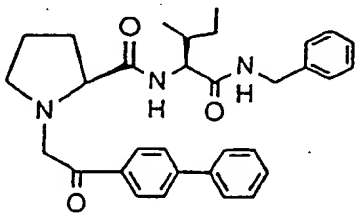
L-Isoleucine, N-[1-(2-Phenyl-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (361 mg, 1.14 mmol), with cesium. carbonate (0.74 g, 2.28 mmol), and 2-bromoacetophenone (1.134 g, 5.69 mmol, 5.0 eq) in acetonitrile (12 mL), provided 466 mg (94%) of the title compound as a pale yellow oil. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (50% ethyl acetate in hexane) = 0.14
R_f (100% ethyl acetate) = 0.54

Example 4



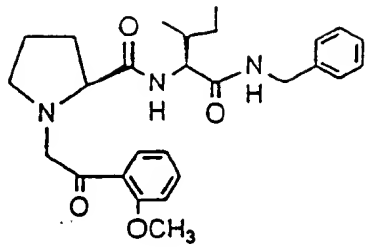
L-Isoleucine, N-[1-(2-Naphth-2-yl-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (296 mg, 0.93 mmol), with cesium carbonate (0.61 g, 1.87 mmol), and 2-bromo-2'-acetonaphthone (697 mg, 2.80 mmol, 3.0 eq) in acetonitrile (12 mL), provided 364 mg (80%) of the title compound as a pale yellow oil. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (50% ethyl acetate in hexane) = 0.25
R_f (100% ethyl acetate) = 0.65

Example 5



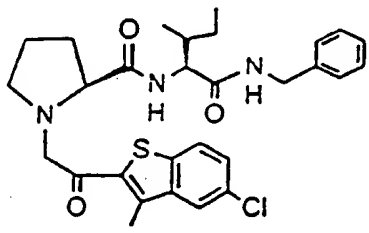
L-Isoleucine, N-[1-(2-Biphenyl-4-yl-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (300 mg, 0.95 mmol), with sodium carbonate (200 mg, 1.89 mmol), and 2-bromo-4'-phenylacetophenone (520 mg, 1.89 mmol, 2.0 eq) in acetonitrile (10 mL), provided 484 mg (87%) of the title compound as a colorless oil. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (100% ethyl acetate) = 0.62

Example 6



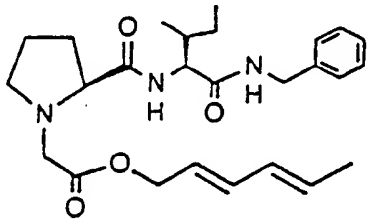
L-Isoleucine, N-[1-(2-(2-Methoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (317 mg, 0.99 mmol), with sodium carbonate (211 mg, 1.99 mmol), and 2-bromo-2'-methoxyacetophenone (457 mg, 1.99 mmol, 2.0 eq) in acetonitrile (10 mL), provided 410 mg (88%) of the title compound as a pale yellow oil. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (100% ethyl acetate) = 0.46
Mass Spectrum (+EI) m/e (rel intensity) 346 (100), 328 (38).

Example 7



L-Isoleucine, N-[1-(2-(5-Chloro-3-Methyl-benzo[B]thiophene-2-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (200 mg, 0.63 mmol), with sodium carbonate (100 mg, 0.94 mmol), and 2-chloroacetyl-5-chloro-3-methylbenzo[B]thiophene (Ryan Scientific; Columbia, SC: 244 mg, 0.941 mmol, 1.5 eq) in acetonitrile (10 mL), provided 170 mg (50%) of the title compound as a pale yellow oil that formed a waxy solid on standing. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (50% ethyl acetate in hexane) = 0.17
R_f (100% ethyl acetate) = 0.66
Mass Spectrum (+EI) m/e (rel intensity) 540 (5, M+), 539 (10), 330 (100).

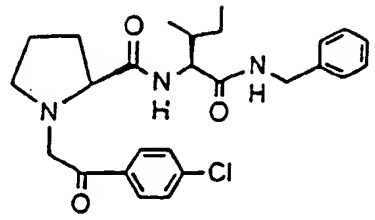
Example 8



L-Isoleucine, N-[1-(2-(trans,trans-Hexa-2,4-dienyl-1-oxy)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (201 mg, 0.63 mmol), with cesium carbonat (412 mg, 1.26 mmol), and 1-(2-chloroacetoxy)-2E,4E-hexadiene (prepared from 2E,4E-hexadien-1-ol and 2-chloro acetylchloride: 221 mg, 1.26 mmol, 2.0 eq) in acetonitril (8 mL), provided 132 mg (46%) of the title compound as a colorl ss oil that formed a waxy solid on standing. The 300 MHz, ^{1}H NMR analysis of this compound was consistent

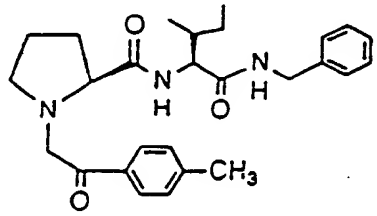
with th structure.
R_f (50% ethyl acetate in hexane) = 0.29
R_f (70% ethyl acetate in hexane) = 0.43
Mass Spectrum (+EI) m/e (rel intensity) 456 (5, M+), 374 (100), 330 (58).

Example 9



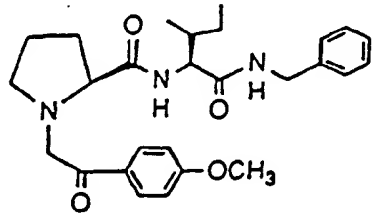
L-Isoleucine, N-[1-(2-(4-Chlorophenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (182 mg, 0.57 mmol), with sodium carbonate (60 mg, 0.57 mmol), and 2-bromo-4'-chloroacetophenone (147 mg, 0.63 mmol, 1.0 eq), in methanol (10 mL), provided 237 mg (88%) of the title compound as a pale yellow oil. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (100% ethyl acetate) = 0.46

Example 10



L-Isoleucine, N-[1-(2-(4-Methylphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (191 mg, 0.60 mmol), with sodium carbonate (70 mg, 0.66 mmol), and 2-bromo-4'-methylacetophenone (141 mg, 0.66 mmol, 1.1 eq), in methanol (5 mL), provided 210 mg (78%) of the title compound as a pale yellow oil. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (70% ethyl acetate in hexane) = 0.30
R_f (100% ethylacetate) = 0.52

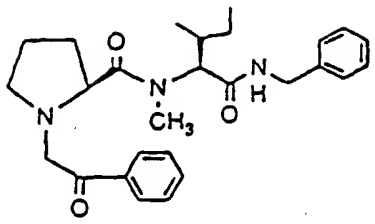
Example 11



L-Isoleucine, N-[1-(2-(4-Methoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (208 mg, 0.65 mmol), with sodium carbonate (104 mg, 0.98 mmol), and 2-bromo-4'-m thoxyacetophenone (195 mg, 0.85 mmol, 1.3 q) in MeOH (10 mL), provided 248 mg (81%) of th titl compound as a pale yellow oil. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with th structur .

R_f (100% ethyl acetate) = 0.40

Example 12

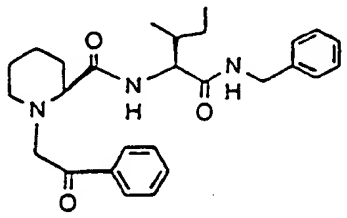


L-Isoleucine, N-Methyl-N-[1-(2-Phenyl-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, 56 mg (0.17 mmol) of L-proline-L-(N-methyl)-isoleucine benzylamide (prepared from N-alpha-t-Boc-N-methyl-L-isoleucine (Schweizerhall, Piscataway, NJ.)) was treated with sodium carbonate (41 mg, 0.40 mmol), and 2-bromoacetophenone (52 mg, 0.26 mmol, 1.5 eq) in methanol (5 mL). A sample of the crude mixture was purified by preparative TLC to provide 2.2 mg of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.

R_f (20% ethyl acetate in dichloromethane) = 0.24

HRMS calcd for $(M+H)^+$ $[(C_{27}H_{36}N_3O_3 + H)^+]$ ion 450.6057; found 450.2760

Example 13

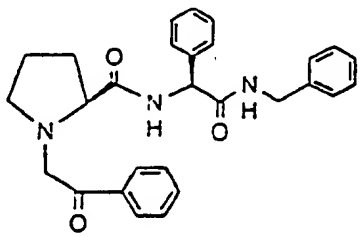


L-Isoleucine, N-[1-(2-Phenyl-2-Oxoethyl)-L-Homoproline] Benzylamide. Using the procedure described in example 1e, 55 mg (0.17 mmol) of L-homoproline-L-isoleucine benzylamide (prepared from L-homoproline (Bachem Bioscience, Philadelphia, PA.)), was treated with sodium carbonate (39 mg, 0.37 mmol), and 2-bromoacetophenone (59 mg, 0.29 mmol, 1.7 eq) in methanol (5 mL). A sample of the crude mixture was purified by preparative TLC to provide 34 mg (45%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.

R_f (20% ethyl acetate in dichloromethane) = 0.31

HRMS calcd for $(M+H)^+$ $[(C_{27}H_{36}N_3O_3 + H)^+]$ ion 450.6057; found 450.2760

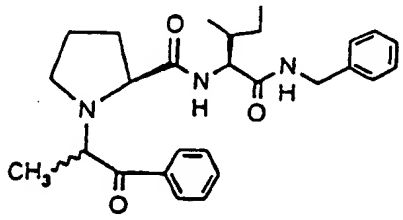
Example 14



L-Phenylglycine, N-[1-(2-Phenyl-2-Oxoethyl)-L-Proline Benzylamide. Using the procedure described in exampl 1e, 285 mg (0.84 mmol) of L-proline-L-phenylglycine benzylamide (prepared from L-phenylglycine. (Bachem Bioscienc , Philadelphia, PA.)),was treated with triethylamine (0.59 mL 4.23 mmol, 5 eq), and 2-bromoacetophenone (185 mg, 0.93 mmol, 1.1 eq) in THF (20 mL). A sample of th crude mixture was purified by preparative TLC to provide 50

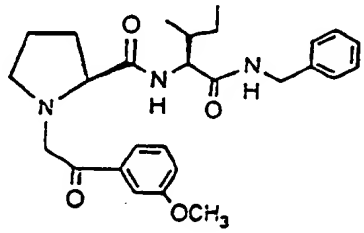
mg of the title compound. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
R_f (50% ethyl acetate in hexane) = 0.09
HRMS calcd for $(M+H)^+$ [$(C_{25}H_{30}N_3O_3 + H)^+$] ion 456.5688; found 456.2289

Example 15



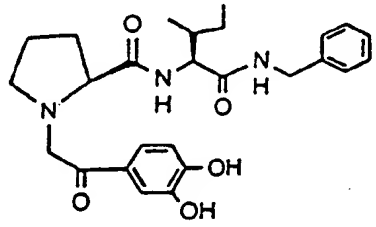
L-Isoleucine, N-[1-(1-Methyl-2-Phenyl-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (196 mg, 0.62 mmol), with sodium carbonate (85 mg, 0.80 mmol), and 2-bromopropiophenone (210 mg, 0.98 mmol, 1.6 eq) in MeOH (12 mL), provided 72 mg (26%) of the title compound. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
R_f (100% ethyl acetate) = 0.54

Example 16



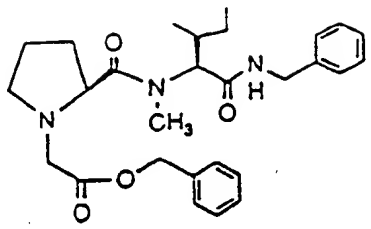
L-Isoleucine, N-[1-(2-(3-Methoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (125 mg, 0.39 mmol), with triethylamine (275 uL, 1.97 mmol, 5 eq), and 2-bromo-3'-methoxyacetophenone (107 mg, 0.47 mmol, 1.2 eq) in THF (20 mL), provided 149.2 mg (81%) of the title compound as a pale yellow oil. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
R_f (50% ethyl acetate in dichloromethane) = 0.32

Example 17



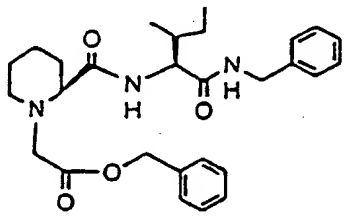
L-Isoleucine, N-[1-(2-(3,4-Dihydroxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (100 mg, 0.31 mmol), with triethylamine (220 uL, 1.58 mmol, 5 eq), and 2-chloro-3'-4'-dihydroxyacetophenone (73 mg, 0.39 mmol, 1.2 eq) in THF (10 mL), provided 54 mg (81%) of the title compound. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
R_f (10% MeOH in dichloromethane) = 0.51

Example 18



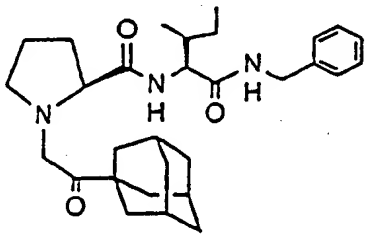
L-Isoleucine, N-Methyl-N-[1-(2-Benzyloxy-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure similiar to that described in example 1e, treatment of L-proline-L-(N-methyl)-isoleucine benzylamide (43 mg, 0.13 mmol), with triethylamine (90 uL, 0.65 mmol, 1.5 eq), and benzyl 2-bromoacetate (52 mg, 0.26 mmol, 2.0 eq) in THF (2.5 mL), provided 90 mg (64%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (50% ethyl acetate in dichloromethane) = 0.43
HRMS calcd for $(M+H)^+$ $[(C_{28}H_{38}N_3O_4 + H)^+]$ ion 480.6328; found 480.2864.

Example 19



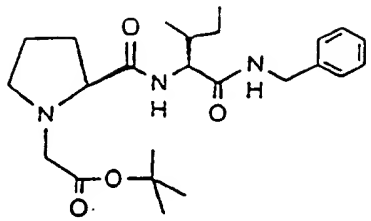
L-Isoleucine, N-[1-(Carbobenzyloxymethylene)-L-Homoproline Benzylamide. Using the procedure described in example 1e, L-homoproline-L-isoleucine benzylamide (43 mg, 0.13 mmol), was treated with triethylamine (91 uL, 0.65 mmol, 1.5 eq), and benzyl 2-bromoacetate (41 uL, 0.26 mmol, 2.0 eq) in THF (2.5 mL). Purification by HPLC provided 54.3 mg of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (50% ethyl acetate in dichloromethane) = 0.52
HRMS calcd for $(M+H)^+$ $[(C_{28}H_{38}N_3O_4 + H)^+]$ ion 480.6328; found 480.2864.

Example 20



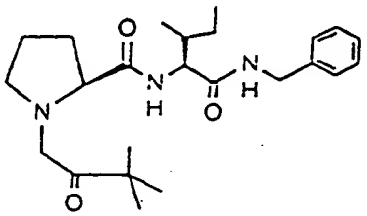
L-Isoleucine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of a solution of L-proline-L-isoleucine benzylamide (160.7 mg, 0.50 mmol), with triethylamine (3.53 mL, 2.53 mmol, 5.0 eq), and 1-adamantyl bromomethyl ketone (156 mg, 0.61 mmol, 1.2 eq) in THF (20 mL), provided 180 mg (99%) of the title compound as a white foam. The 300 MHz, ^{1}H NMR analysis of this compound was consist nt with th structure.
R_f (50% dichloromethan in ethyl acetate) = 0.45
HRMS calcd for $(M+H)^+$ $[(C_{30}H_{44}N_3O_3 + H)^+]$ ion 494.7030; found 494.3385.

Example 21



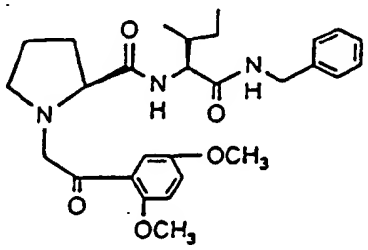
L-Isoleucine, N-[1-(Carbo-tert-Butoxymethylene)-L-Proline] Benzylamide. Using the procedure described in example 1e, treatment of a solution of L-proline-L-isoleucine benzylamide (66 mg, 0.21 mmol), with triethylamine (147 uL, 1.05 mmol, 5.0 eq), and alpha-bromo-tert-butylacetate (68 uL, 0.42 mmol, 2 eq) in THF (5 mL), provided 70 mg (77%) of the title compound. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
R_f (50% dichloromethane in ethyl acetate) = 0.51
HRMS calcd for $(M+H)^+$ $[(C_{24}H_{38}N_3O_4 + H)^+]$ ion 432.5884; found 432.2864

Example 22



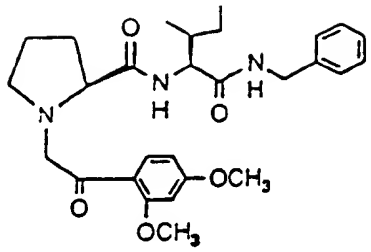
L-Isoleucine, N-[1-(2-tert-Butyl-2-Oxoethyl)-L-Proline] Benzylamide. Using the procedure described in example 1e, treatment of a solution of L-proline-L-isoleucine benzylamide (69 mg, 0.21 mmol), with triethylamine (151 uL, 1.08 mmol, 5.0 eq), and 1-bromopinacolone (58 uL, 0.43 mmol, 2 eq) in THF (5 mL), provided 35 mg (39%) of the title compound as a colorless oil. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
R_f (50% dichloromethane in ethyl acetate) = 0.42
HRMS calcd for $(M+H)^+$ $[(C_{24}H_{38}N_3O_4 + H)^+]$ ion 416.5863; found 416.2915

Example 23



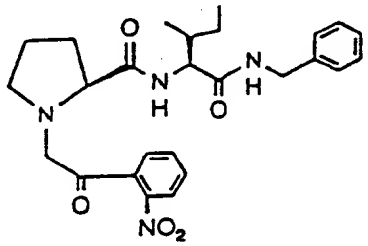
L-Isoleucine, N-[1-(2-(2,5-Dimethoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of a solution of L-proline-L-isoleucine benzylamide (51 mg, 0.16 mmol), with triethylamine (113 uL, 0.81 mmol, 5.0 eq), and 2-bromo-2'-5'-dimethoxyacetophenone (50 mg, 0.19 mmol, 1.2 eq) in THF (5 mL), provided 60 mg (75%) of the title compound as a colorless oil. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
R_f (50% dichloromethane in ethyl acetate) = 0.36
HRMS calcd for $(M+H)^+$ $[(C_{28}H_{38}N_3O_5 + H)^+]$ ion 496.6307; found 496.2813

Example 24



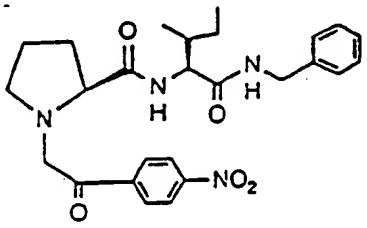
L-Isoleucine, N-[1-(2-(2,4-Dimethoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of a solution of L-proline-L-isoleucine benzylamide (51 mg, 0.16 mmol), with triethylamine (112 uL, 0.81 mmol, 5.0 eq), and 2-bromo-2'-4'-dimethoxyacetophenone (50 mg, 0.19 mmol, 1.2 eq) in THF (5 mL), provided 55 mg (70%) of the title compound as a colorless oil. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (50% dichloromethane in ethyl acetate) = 0.34

Example 25



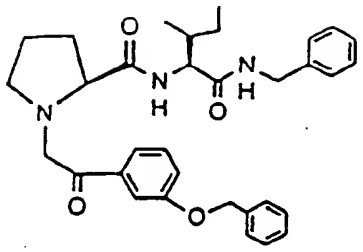
L-Isoleucine, N-[1-(2-(2-Nitrophenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of a solution of L-proline-L-isoleucine benzylamide (54 mg, 0.17 mmol), with triethylamine (118 uL, 0.84 mmol, 5.0 eq), and 2-bromo-2'-nitroacetophenone (50 mg, 0.20 mmol, 1.2 eq) in THF (5 mL), provided 46 mg (57%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (50% dichloromethane in ethyl acetate) = 0.29

Example 26



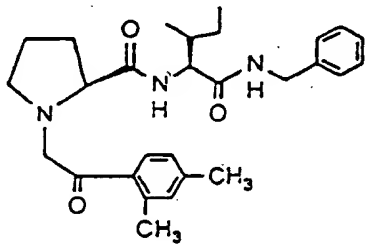
L-Isoleucine, N-[1-(2-(4-Nitrophenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of a solution of L-proline-L-isoleucine benzylamide (50 mg, 0.16 mmol), with triethylamine (110 uL, 0.79 mmol, 5.0 eq), and 2-bromo-4'-nitroacetophenone (48 mg, 0.20 mmol, 1.2 eq) in THF (5 mL), provided crude material that was additionally purified by preparative TLC to provide 8.8 mg (12%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (50% dichloromethane in ethyl acetate) = 0.30
HRMS calcd for $(M+H)^+$ [$(C_{26}H_{33}N_4O_5 + H)^+$] ion 481.5754; found 481.2453

Example 27



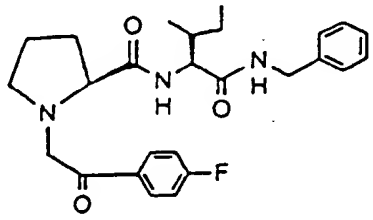
L-Isoleucine, N-[1-(2-(3-Benzyloxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of a solution of L-proline-L-isoleucine benzylamide (111 mg, 0.35 mmol), with triethylamine (245 uL, 1.75 mmol, 5.0 eq), and 2-bromo-3'-benzloxyacetophenone (129 mg, 0.42 mmol, 1.2 eq) in THF (10 mL), provided 147 mg (76%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (50% dichloromethane in ethyl acetate) = 0.38
HRMS calcd for (M+H)$^+$ [($C_{33}H_{40}N_3O_4$ + H)$^+$] ion 542.7028; found 542.3021

Example 28



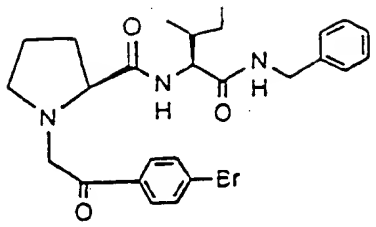
L-Isoleucine, N-[1-(2-(2,4-Dimethylphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of a solution of L-proline-L-isoleucine benzylamide (60 mg, 0.19 mmol), with triethylamine (130 uL, 0.94 mmol, 5.0 eq), and 2-bromo-2',4'-dimethylacetophenone (52 mg, 0.23 mmol, 1.2 eq) in THF (7 mL), provided a crude product. A portion of the product was purified by preparative TLC to provide 19 mg (21%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (50% dichloromethane in ethyl acetate) = 0.38
HRMS calcd for (M+H)$^+$ [($C_{28}H_{38}N_3O_3$ + H)$^+$] ion 464.6319; found 464.2915

Example 29



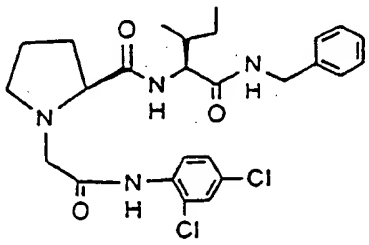
L-Isoleucine, N-[1-(2-(4-Fluorophenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of a solution of L-proline-L-isoleucine benzylamide (56 mg, 0.18 mmol), with triethylamine (123 uL, 0.88 mmol, 5.0 eq), and 2-bromo-4'-fluoroacetophenone (37 mg, 0.21 mmol, 1.2 eq) in THF (7 mL), provided a crud product. A portion of the product was purified by preparative TLC to provid 28 mg (35%) of the title compound. The 300 MHz, ^{1}H NMR analysis f this compound was consistent with the structure.
R_f (50% dichloromethane in ethyl acetate) = 0.35

Example 30



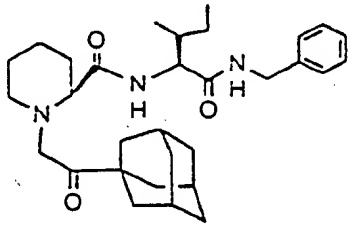
L-Isoleucine, N-[1-(2-(4-Bromophenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of a solution of L-proline-L-isoleucine benzylamide (57 mg, 0.18 mmol), with triethylamine (130 uL, 0.93 mmol, 5.0 eq), and 2,-4'-dibromoacetophenone (63 mg, 0.22 mmol, 1.2 eq) in THF (7 mL), provided a crude product. A portion of the product was purified by preparative TLC to provide 62 mg (67%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (10% MeOH in dichloromethane) = 0.70

Example 31



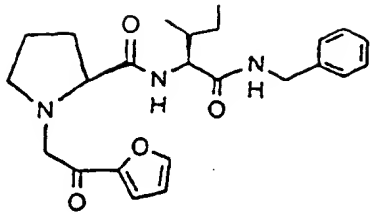
L-Isoleucine, N-[1-(2,4-Dichlorophenylcarbamoylmethyl)-L-Proline] Benzylamide. Using the procedure described in example 1e, treatment of a solution of L-proline-L-isoleucine benzylamide (58 mg, 0.18 mmol), with triethylamine (130 uL, 0.93 mmol, 5.0 eq), and N-chloroacetyl-2,4-dichloroaniline (53 mg, 0.22 mmol, 1.2 eq) in THF (7 mL), provided a crude product. A portion of the product was purified by preparative TLC to provide 30 mg (32%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (10% MeHO in dichloromethane) = 0.70

Example 32



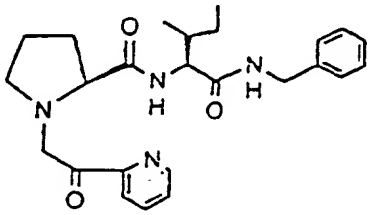
L-Isoleucine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Homoproline] Benzylamide. Using the procedure described in example 1e, L-homoproline-L-isoleucine benzylamide (75 mg, 0.22 mmol), was treated with triethylamine (0.15 mL, 1.12 mmol, 5 eq), 1-adamantyl bromomethyl ketone (92 mg, 0.36 mmol, 1.6 eq), and THF (10 mL), to provide 64 mg (56%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (50% ethyl acetat in dichlor methane) = 0.56
HRMS calcd for $(M+H)^+$ [$(C_{31}H_{46}N_3O_3 + H)^+$] ion 508.7290; found 508.3532

Example 33



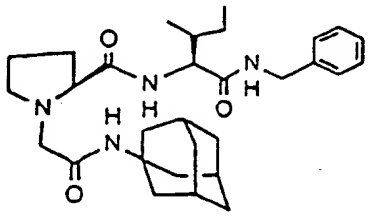
L-Isoleucine, N-[1-(2-Furan-2-yl-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, a solution of L-proline-L-isoleucine benzylamide (114 mg, 0.36 mmol), and triethylamine (0.10 mL, 0.78 mmol, 2.0 eq), in THF (10 mL),was treated with 255 mg (1.76 mmol, 5.0 eq) of 2-(alpha-chloroacyl)furan (prepared from 2-furoic acid) to provide 130 mg, (85%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (100% ethyl acetate) = 0.25

Example 34



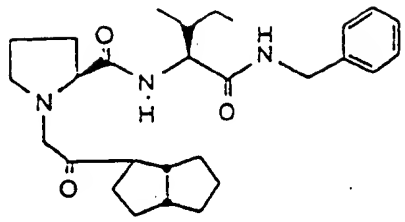
L-Isoleucine, N-[1-(2-Pyrid-2-yl-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, a solution of L-proline-L-isoleucine benzylamide (148 mg, 0.47 mmol), and triethylamine (0.13 mL, 0.93 mmol, 2.0 eq) in THF (10 mL), was treated with 234 mg (1.50 mmol) of 2-(alpha-chloroacyl)pyridine (prepared from picolinic acid) to provide 20 mg, (10%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
Rf (50% ethyl acetate in hexane) 0.47

Example 35



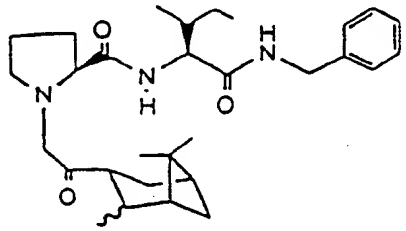
L-Isoleucine, N-[1-(Adamant-1-ylcarbamoylmethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, a solution of L-proline-L-isoleucine benzylamide (115 mg, 0.36 mmol), and triethylamine (253 uL, 1.8 mmol, 5.0 eq) in THF (5 mL) was treated with 93 mg (0.43 mmol) of N-(alpha-chloroacyl)1-aminoadamantane (prepared from 1-adamantanamine and 2-chloroacetyl chloride) to provide 135 mg, (73%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
Rf (100% ethyl acetate) = 0.12
HRMS calcd for $(M+H)^+$ $[(C_{30}H_{45}N_4O_3 + H)^+]$ ion 509.7166; found 509.3494

Example 36



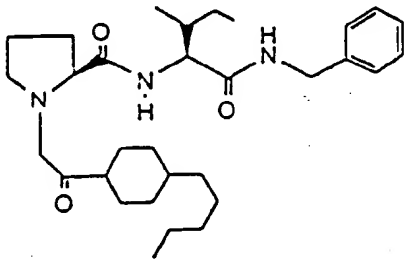
L-Isoleucine, N-[1-(2-(cis-Octahydro-pentalen-1-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, a solution of L-proline-L-isoleucine benzylamide (115 mg, 0.36 mmol), and triethylamine (346 uL, 2.5 mmol, 5.0 eq), in THF (2 mL), was treated with 181 mg (0.97 mmol) of 1-chloro-2-(octahydro-pentalen-1-yl)-2-oxoethane (prepared from cis-bicyclo[3.3.0]octane-2-carboxylic acid) to provide 52 mg, (23%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
Rf (50% ethyl acetate in dichloromethane) = 0.36

Example 37



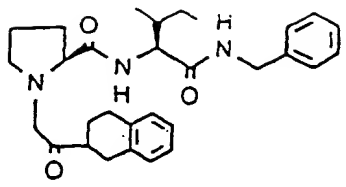
L-Isoleucine, N-[1-[2-(2,6,6-Trimethyl-Bicyclo[3.1.1]hept-3-yl)-2-Oxoethyl]-L-Prolyl] Benzylamide. Using the procedure described in example 1e, a solution of L-proline-L-isoleucine benzylamide (153 mg, 0.48 mmol) and triethylamine (337 uL, 5.0 eq), in THF (2 mL), was treated with 205 mg (0.95 mmol) of 1-chloro-2-(2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)-2-oxoethane (prepared from (-)-3-pinanecarboxylic acid) to provide 164 mg, (68%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
Rf (50% ethyl acetate in dichloromethane) = 0.42

Example 38



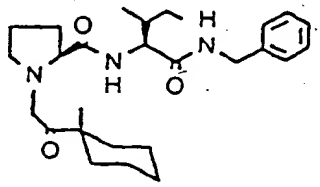
L-Isoleucine, N-[1-(2-(4-Pentylcyclohexyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, a solution of L-proline-L-isoleucine benzylamide (160 mg, 0.50 mmol), and triethylamine (352 uL, 2.53 mmol, 5.0 eq), in THF (2 mL), was treated with 232 mg (1.0 mmol) of 1-chloro-2-(4-pentylcyclohexyl)-2-oxoethane (prepared from trans-4-pentylcyclohexanecarboxylic acid) to provide 154 mg (25%) of the title compound. Th 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
Rf (50% ethyl ac tate in dichloromethan) = 0.45

Example 39



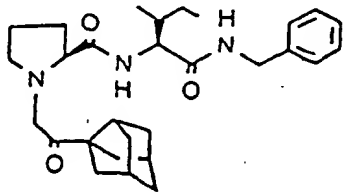
L-Isoleucine, N-[1-(2-(1,2,3,4-tetrahydro-Napththalen-2-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, a solution of L-proline-L-isoleucine benzylamide (162 mg, 0.51 mmol), and triethylamine (355 uL, 5.0 eq), THF (2 mL), was treated with 212 mg (2.0 eq) of 1-chloro-2-(1,2,3,4-tetrahydro-napththalen-2-yl)-2-oxoethane (prepared from 1,2,3,4-tetrahydro-2-napththoic acid) to provide 191 mg (77%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
Rf (50% ethyl acetate in dichloromethane) = 0.42

Example 40



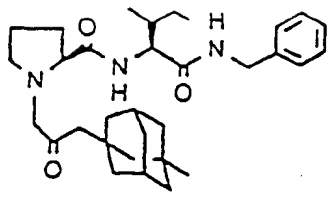
L-Isoleucine, N-[1-(2-(1-Methyl-Cyclohexyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, a solution of L-proline-L-isoleucine benzylamide (164 mg, 0.51 mmol), and triethylamine (355 uL, 5.0 eq) in THF (2 mL), was treated with 180 mg (2.0 eq) of 1-chloro-2-(1-methyl-cyclohexyl)-2-oxoethane (prepared from 1-methyl-1-cyclohexanecarboxylic acid) to provide 183 mg (93%) of the title compound as a colorless residue. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
Rf (66% ethyl acetate in hexane) = 0.32

Example 41



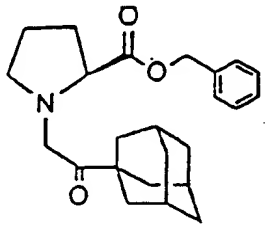
L-Isoleucine, N-[1-(2-Oxo-2-Tricyclo[3.3.1.0 ^{3,7}]Non-3-yl-Ethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, a solution of L-proline-L-isoleucine benzylamide (167 mg, 0.52 mmol), and triethylamine (367 uL, 5.0 eq) in THF (2 mL), was treated with 209 mg (1.2 eq) of 1-chloro-2-oxo-2-tricyclo[3.3.1.0 ^{3,7}]non-3-yl-ethane (prepared from 3-noradamantanecarboxylic acid) to provide 181 mg of the title compound as a colorless residue. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
Rf (9% methanol in dichloromethane) = 0.70

Example 42



L-Isoleucine, N-[1-(2-Oxo-3-(3-Methyl-Adamantan-1-yl)-Propyl)-L-Prolyl] Benzylamide. Using the procedur described in example 1e, a solution of L-proline-L-isoleucine benzylamide (162 mg, 0.51 mmol), and triethylamine (358 uL, 5.0 eq), in THF (2 mL), was treated with 246 mg (1.0 eq) of 1-chloro-2-oxo-3-(3-methyl-adamantan-1-yl)-propan (prepared from 3-methyl-1-adamantaneacetic acid) to provide 210 mg (78%) of the title compound as a colorless residue. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
Rf (50% ethyl acetate in hexane) = 0.43

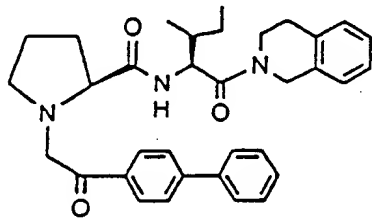
Example 43 (Not within the scope of the claims)



L-Proline, 1-(2-Adamantan-1-yl-2-Oxoethyl) Benzyl Ester. Using the procedure described in example 1e, a solution containing the hydrochloride salt of L-proline benzyl ester (25.46 g, 105.3 mmol), triethylamine (58.0 mL, 414 mmol, 4.0 eq), 1-adamantyl bromomethyl ketone (26.6 g, 103.4 mmol, 1.0 eq) and THF (500 mL), was warmed to reflux, cooled, and purified by flash chromatography to provide 30.0 g (76%) of the title compound as a white foam. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (50% dichloromethane in ethyl acetate) = 0.42

Example 44

L-Isoleucine, N-[1-(2-(Biphenyl-4-yl)-2-Oxoethyl)-L-Prolyl] 1,2,3,4-Tetrahydroisoquinolinamide.



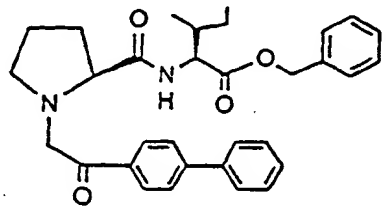
a) N-[2-(Biphenyl-4-yl)-2-Oxoethyl] L-Proline Benzyl Ester. Using the procedure described in Example 1e, a solution of the hydrochloride salt of L-proline benzyl ester (20.75 g, 98.0 mmol), was treated with cesium carbonate (87.1 g, 267 mmol, 3.0 eq), 2-bromo-4'-phenylacetophenone (24.5 g, 89.0 mmol, 1.0 eq) in acetonitrile (500 mL), to provide 10.07 g (28%) of L-proline, N-[2-(biphenyl-4-yl)-2-oxoethyl] benzyl ester.

b) N-[2-(Biphenyl-4-yl)-2-Oxoethyl] L-Proline. A solution of N-[2-(biphenyl-4-yl)-2-oxoethyl] L-proline benzyl ester in methanol (300 mL) and tr ated with 10% palladium on carbon (908 mg). Hydrogenation as describ d in example 1d, followed by recrystallization from ethyl ether provided 1.72 g (6.2 % overall) of the titl compound as a whit

solid. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
mp = 182-184 °C
R_f (17% MeOH in dichloromethane) = 0.38

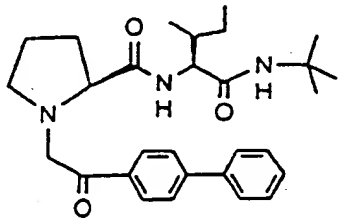
c) L-Isoleucine, N-[1-(2-(Biphenyl-4-yl)-2-Oxoethyl)-L-Prolyl] 1,2,3,4-Tetrahydroisoquinolinamide. A solution of N-[2-(biphenyl-4-yl)-2-oxoethyl] L-proline (50 mg, 0.16 mmol, 1.0 eq), N-ethylmorpholine (125 uL, 0.97 mmol, 6 eq) in acetonitrile (0.5 mL) was cooled to 0 °C and treated with a 50% solution of 1-n-propylphosphonic acid cyclic anhydride in dichloromethane (170 uL, 0.26 mmol, 1.6 eq) followed by the L-isoleucine 1,2,3,4-tetrahydroisoquinolinamide (prepared as described in example 1a; 47.9 mg, 0.19 mmol, 1.2 eq). Purification by HPLC procided 5.53 mg (6.3 %) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
Rf (50 % ethyl acetate in hexane)= 0.51
HRMS calcd for $(M+H)^+$ $[(C_{34}H_{40}N_3O_3 + H)^+]$ ion 538.7154; found 538.3072

Example 45 (Not within the scope of the claims)



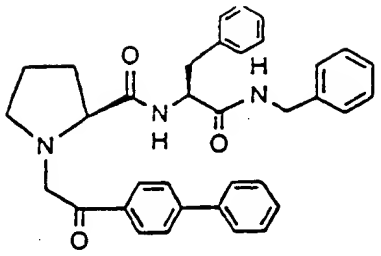
L-Isoleucine, N-[1-(2-(Biphenyl-4-yl)-2-Oxoethyl)-L-Prolyl] Benzyl Ester. A solution of N-[2-(biphenyl-4-yl)-2-oxoethyl] L-proline (102 mg, 0.33 mmol, 1.0 eq), N-ethylmorpholine (270 uL, 2.12 mmol, 6.4 eq) in acetonitrile (1.0 mL) was cooled to 0 °C and treated with a 50% solution of 1-n-propylphosphonic acid cyclic anhydride in dichloromethane (340 uL, 0.53 mmol, 1.6 eq) followed by the tosylate salt of L-isoleucine benzyl ester (143 mg, 0.36 mmol, 1.1 eq). Purification by HPLC provided 45 mg (26%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
Rf 50 % ethyl acetate in hexane)= 0.29

Example 46



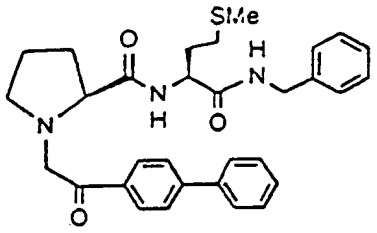
L-Isoleucine, N-[1-(2-(Biphenyl-4-yl)-2-Oxoethyl)-L-Prolyl] tert-Butylamide. A solution of N-[2-(biphenyl-4-yl)-2-oxoethyl] L-proline (50 mg, 0.16 mmol, 1.0 eq), N-ethylmorpholine (125 uL, 0.98 mmol, 6 eq) in acetonitrile (0.5 mL) was cooled to 0 °C and treated with a 50% solution of 1-n-propylphosphonic acid cyclic anhydride in dichloromethan (170 uL, 0.27 mmol, 1.6 eq) followed by L-isoleucine tert-butylamide (49 mg, 0.19 mmol, 1.1 eq). Purification by HPLC provided 12 mg (16%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
Rf 50 % ethyl acetate in hexane)= 0.38
HRMS calcd for $(M+H)^+$ $[(C_{29}H_{40}N_3O_3 + H)^+]$ ion 478.6604; found 478.3072

Example 47



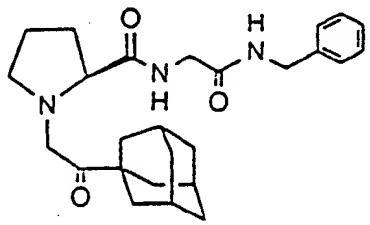
L-Phenylalanine, N-[1-(2-(Biphenyl-4-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide. A solution of N-[2-(biphenyl-4-yl)-2-oxoethyl] L-proline (51 mg, 0.16 mmol, 1.0 eq), N-ethylmorpholine (125 uL, 0.98 mmol, 6 eq) in acetonitrile (0.5 mL) was cooled to 0 °C and treated with a 50% solution of 1-n-propylphosphonic acid cyclic anhydride in dichloromethane (170 uL, 0.27 mmol, 1.6 eq) followed by phenylalanine benzylamide (49 mg, 0.19 mmol, 1.1 eq). Purification by HPLC provided 12 mg (14%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
Rf 50 % ethyl acetate in hexane)= 0.38

Example 48



L-Methionine, N-[1-(2-(Biphenyl-4-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide. A solution of N-[2-(biphenyl-4-yl)-2-oxoethyl] L-proline (54 mg, 0.17 mmol, 1.0 eq), N-ethylmorpholine (133 uL, 1.04 mmol, 6 eq) in acetonitrile (0.5 mL) was cooled to 0 °C and treated with a 50% solution of 1-n-propylphosphonic acid cyclic anhydride in dichloromethane (180 uL, 0.27 mmol, 1.6 eq) followed by the L-methionine benzylamide (71.36 mg, 0.30 mmol, 1.7 eq). Purification by HPLC provided 35 mg (38%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
Rf 50 % ethyl acetate in hexane) = 0.40
HRMS calcd for $(M+H)^+$ $[(C_{31}H_{35}N_3O_3S + H)^+]$ ion 530.711; found 530.2480

Example 49

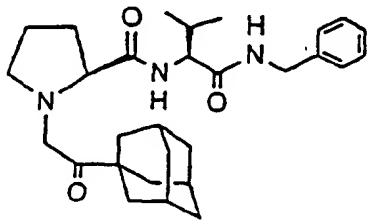


Glycine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide.

a) 1-(2-Adamantan-1-yl-2-Oxoethyl) L-Proline. Using the procedure described in example 1d, a solution of L-prolin , 1-(2-adamantan-1-yl-2-oxoethyl) benzyl ester (30.0 g, 76.63 mmol), 10% palladium on carbon (4.2 g), and

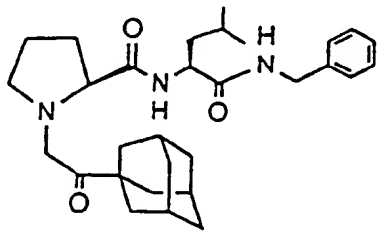
methanol (100 mL) was purged with hydrogen, and stirred under an atmospher of hydrogen until no more benzyl ester was observed by TLC. The solution was purged with argon, filtered through a plug of celite, and concentrated in vacuo, and recrystallized from ethyl ether to provide 19.45 g, (85%) of the title compound as a white solid. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
mp 130-142 (sweat), 143-145 (melt)
R_f (20% MeOH in dichloromethane) = 0.32
b) Glycine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1a, a solution of 1-(2-adamantan-1-yl-2-oxoethyl) L-proline (104.6 mg, 0.36 mmol, 1.0 eq), triethylamine (150 uL, 1.07 mmol, 3.0 eq), and THF (1.5 mL), was treated with isobutyl chloroformate (51 uL, 0.39 mL, 1.1 eq), then with glycine N-benzylamide (88.2 mg, 537 umol, 1.5 eq). Workup as before provided 53.9 mg (34%) of the title compound as a white foam. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (50 % ethyl acetate in dichloromethane) = 0.22

Example 50



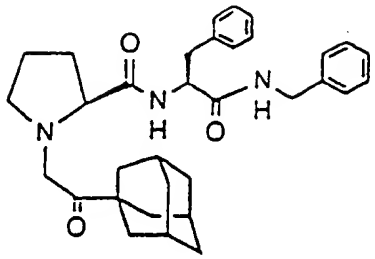
L-Valine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1a, a solution of 1-(2-adamantan-1-yl-2-oxoethyl) L-proline (109.1 mg, 0.37 mmol, 1.0 eq), triethylamine (156 uL, 1.12 mmol, 3.0 eq), and THF (1.5 mL), was treated with isobutyl chloroformate (53 uL, 0.41 mL, 1.1 eq), then with L-valine benzylamide (117.5 mg, 570 umol, 1.5 eq). Workup as before provided 127 mg (71%) of the title compound as a white foam. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (50 % ethyl acetate in dichloromethane) = 0.40

Example 51



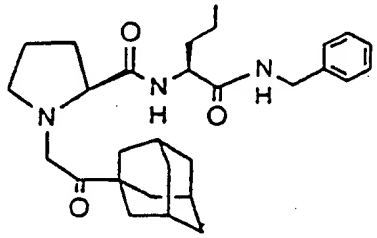
L-Leucine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described previously, a solution of 1-(2-adamantan-1-yl-2-oxoethyl) L-proline (108 mg, 0.37 mmol, 1.0 eq), triethylamine (156 uL, 1.11 mmol, 3.0 eq), and THF (1.5 mL), was treated with isobutyl chloroformate (53 uL, 0.41 mL, 1.1 eq), then with L-leucine N-benzylamide (123 mg, 570 umol, 1.5 eq). Workup as before provided 124 mg (68%) of the title compound. The 300 NHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (50 % ethyl acetate in dichloromethane) = 0.48

Example 52



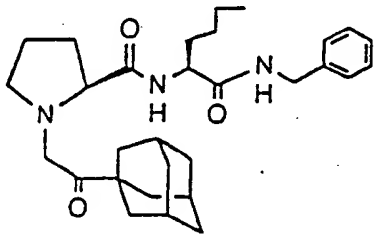
L-Phenylalanine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described previously, a solution of 1-(2-adamantan-1-yl-2-oxoethyl) L-proline (100 mg, 0.34 mmol, 1.0 eq), L-phenylalanine N-benzylamide (175 mg, 686 umol, 2.0 eq) and dichloromethane (1.0 mL), was cooled to 0 °C, and treated with triethylamine (286 uL, 2.0 mmol, 6.0 eq). To this chilled solution was added a 50 % solution of 1-n-propylphosphonic acid cyclic anhydride in dichloromethane (436 uL, 0.68 mL, 2.0 eq). When TLC indicated the reaction was complete, the solution was allowed to warm to 22 °C, washed with satd aq $NaHCO_3$, concentrated in vacuo, and purified by flash chromatography to provide 144 mg (80%) of the title compound. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
R_f (50 % ethyl acetate in dichloromethane) = 0.36

Example 53



L-Norvaline, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described previously, a solution of 1-(2-adamantan-1-yl-2-oxoethyl)L-proline (155 mg, 0.53 mmol, 1.0 eq), L-norvaline N-benzylamide (220 mg, 1.07 mmol, 2.0 eq) and dichloromethane (1.0 mL), was treated with triethylamine (446 uL, 3.2 mmol, 6.0 eq), and a 50 % solution of 1-n-propylphosphonic acid cyclic anhydride in dichloromethane (680 uL, 1.07 mL, 2.0 eq), to provide 372 mg (70%) of the title compound. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
R_f (50 % ethyl acetate in dichloromethane) = 0.37

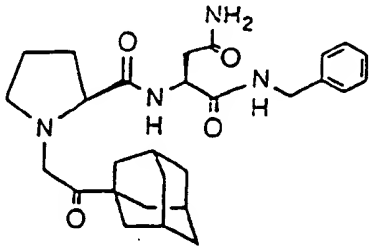
Example 54



L-Norleucine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described previously, a solution of 1-(2-adamantan-1-yl-2-oxo thyl) L-proline (154 mg, 0.53 mmol, 1.0 eq), L-norleucine N-benzylamide (234 mg, 1.07 mmol, 2.0 eq) and dichloromethane (1.0 mL), was treated with triethylamine (446 uL, 3.2 mmol,

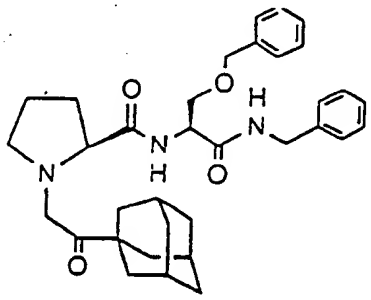
6.0 eq), and a 50 % solution of 1-n-propylphosphonic acid cyclic anhydride in dichloromethane (680 uL, 1.07 mL, 2.0 eq), to provide 210 mg (80%) of the title compound as a white foam. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (50 % ethyl acetate in dichloromethane) = 0.44

Example 55



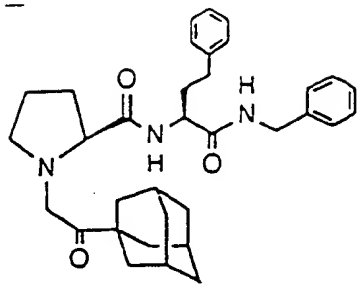
L-Asparagine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described previously, heterogeneous solution of 1-(2-adamantan-1-yl-2-oxoethyl) L-proline (152 mg, 0.52 mmol, 1.0 eq), L-asparagine.N-benzylamide (231 mg, 1.04 mmol, 2.0 eq) and dichloromethane (1.5 mL), was treated with triethylamine (436 uL, 3.1 mmol, 6.0 eq), and a 50 % solution of 1-n-propylphosphonic acid cyclic anhydride in dichloromethane (663 uL, 1.04 mL, 2.0 eq), to provide 130.7 mg (51%) of the title compound as a white foam. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (10% MeOH in dichloromethane) = 0.41

Example 56



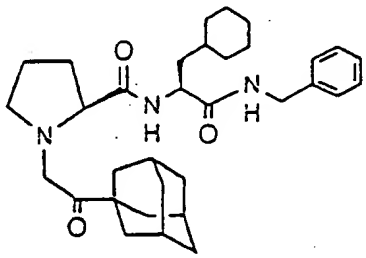
L-Serine-(O-Benzyl Ether), N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described previously, a solution of 1-(2-adamantan-1-yl-2-oxoethyl) L-proline (151 mg, 0.52 mmol, 1.0 eq), L-serine-(O-benzyl ether)-N-benzylamide (294 mg, 1.03 mmol, 2.0 eq) and dichloromethane (1.5 mL), was treated with triethylamine (432 uL, 3.1 mmol, 6.0 eq), and a 50 % solution of 1-n-propylphosphonic acid cyclic anhydride in dichloromethane (658 uL, 2.0 eq), to provide 220 mg (76%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (50% ethyl acetate in dichloromethane) = 0.30

Example 57



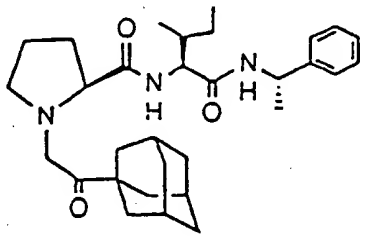
L-β-Phenylalanine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described previously, a solution of 1-(2-adamantan-1-yl-2-oxoethyl) L-proline (154 mg, 0.53 mmol, 1.0 eq), L-β-phenylalanine N-benzylamide (286 mg, 1.06 mmol, 2.0 eq) and dichloromethane (1.5 mL), was treated with triethylamine (442 uL, 3.2 mmol, 6.0 eq), and a 50 % solution of 1-n-propylphosphonic acid cyclic anhydride in dichloromethane (673 uL, 2.0 eq), to provide 229 mg (81%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (50% ethyl acetate in dichloromethane) = 0.40

Example 58



L-Cyclohexylalanine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described previously, a solution of 1-(2-adamantan-1-yl-2-oxoethyl) L-proline (155 mg, 0.53 mmol, 1.0 eq), L-cyclohexylalanine N-benzylamide (248 mg) and dichloromethane (1.5 mL), was treated with triethylamine (444 uL, 3.2 mmol, 6.0 eq), and a 50 % solution of 1-n-propylphosphonic acid cyclic anhydride in dichloromethane (676 uL, 2.0 eq), to provide 148 mg (52%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (50% ethyl acetate in dichloromethane) = 0.42

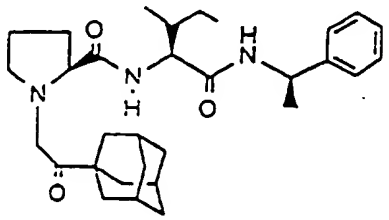
Example 59



L-Isoleucine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] alpha-(S)-methylbenzylamide. Using the procedure described previously, a solution of 1-(2-adamantan-1-yl-2-oxoethyl) L-proline (154 mg, 0.53 mmol, 1.0 eq), L-isoleucine alpha-(S)-methylbenzylamide (247 mg, 1.05 mmol) and dichloromethane (1.5 mL), was treated with triethyl-

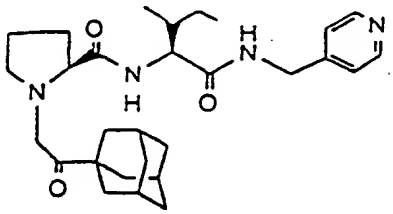
amine (441 uL, 3.2 mmol, 6.0 eq), and a 50 % solution of 1-n-propylphosphonic acid cyclic anhydride in dichloromethane (671 uL, 2.0 q), to provide 192 mg (72%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (50 % ethyl acetate in dichloromethane) = 0.44

Example 60



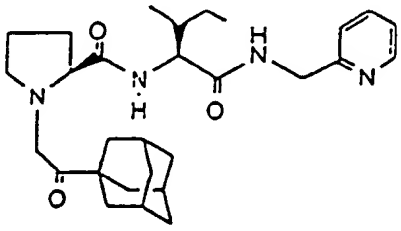
L-Isoleucine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] alpha-(R)-methylbenzylamide. Using the procedure described previously, a solution of 1-(2-adamantan-1-yl-2-oxoethyl) L-proline (146 mg, 0.53 mmol, 1.0 eq), L-isoleucine alpha-(R)-methylbenzylamide (234 mg, 1.05 mmol) and dichloromethane (1.5 mL), was treated with triethylamine (420 uL, 6.0 eq), and a 50 % solution of 1-n-propylphosphonic acid cyclic anhydride in dichloromethane (638 uL, 2.0 eq), to provide 108 mg (43%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (15% methanol in dichloromethane) = 0.47

Example 61



L-Isoleucine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Pyridin-4-ylmethylamide. Using the procedure described previously, a solution of 1-(2-adamantan-1-yl-2-oxoethyl) L-proline (230 mg, 0.78 mmol, 1.0 eq), L-isoleucine pyridin-4-ylmethylamide (266 mg, 1.5 mmol) and dichloromethane (2 mL), was treated with triethylamine (660 uL, 6.0 eq), and a 50 % solution of 1-n-propylphosphonic acid cyclic anhydride in dichloromethane (1.0 mL, 2.0 eq), to provide 180 mg (46%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (4% methanol in dichloromethane) = 0.23

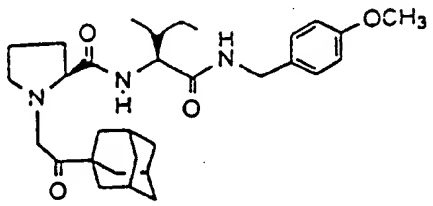
Example 62



L-Isoleucin , N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Pyridin-2-ylmethylamide. Using the procedure d scribed previously, a solution of 1-(2-adamantan-1-yl-2-oxoethyl) L-prolin (165 mg, 0.56 mmol, 1.0 eq), L-isol ucine pyridin-2-ylmethylamide (246 mg, 1.11 mmol) and dichloromethan (2 mL), was treated with triethylamine (475 uL, 6.0

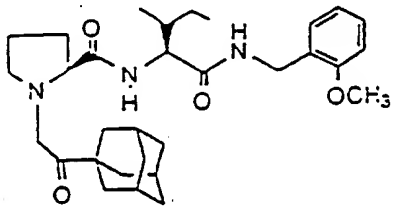
eq), and a 50 % solution of 1-n-propylphosphonic acid cyclic anhydride in dichloromethane (721 uL, 2.0 eq), to provide 214 mg (77%) of th title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure. R_f (5% methanol in dichloromethane) = 0.21

Example 63



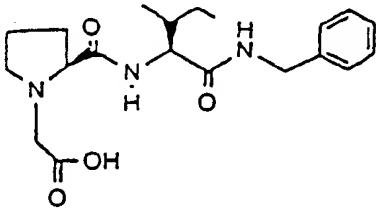
L-Isoleucine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] 4-methoxybenzylamide. Using the procedure described previously, a solution of 1-(2-adamantan-1-yl-2-oxoethyl) L-proline (140 mg, 0.48 mmol, 1.0 eq), L-isoleucine 4-methoxybenzylamide (238 mg, 0.95 mmol) and dichloromethane (2 mL), was treated with triethylamine (400 uL, 6.0 eq), and a 50 % solution of 1-n-propylphosphonic acid cyclic anhydride in dichloromethane (610 uL, 2.0 eq), to provide 207 mg (82%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure. R_f (50% ethyl acetate in dichloromethane) = 0.31

Example 64



L-Isoleucine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] 2-methoxybenzylamide. Using the procedure described previously, a solution of 1-(2-adamantan-1-yl-2-oxoethyl) L-proline (179 mg, 0.61 mmol, 1.0 eq), L-isoleucine 2-methoxybenzylamide (308 mg, 1.23 mmol) and dichloromethane (2 mL), was treated with triethylamine (515 uL, 6.0 eq), and a 50 % solution of 1-n-propylphosphonic acid cyclic anhydride in dichloromethane (783 uL, 2.0 eq), to provide 254 mg (79%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure. R_f (50% ethyl acetate in dichloromethane) = 0.31

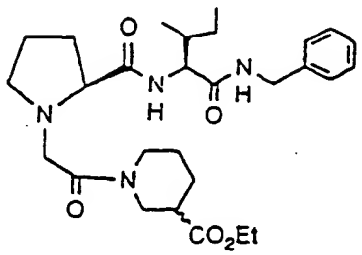
Example 65



L-Isoleucine, N-[1-(Carboxymethyl)-L-Prolyl] Benzylamide. Using the hydrogenation conditions described in example 1d, a solution of L-isoleucine, N-[1-(2-benzyloxy-2-oxoethyl)-L-prolyl] benzylamide (14.80 g, 31.76 mmol), 10% palladium on carbon (0.80 g), and methanol (350 mL), was purged with hydrogen, and stirred under an atmosphere of hydrogen at 22 °C. After 8 hrs, the solution was purged with argon, filtered through a plug of celite, and concentrated in vacuo to provide 11.47 g (96%) of the title compound as a white solid. The 300 MHz, ^{1}H NMR and mass spectrum analysis of this compound was consist nt with th structure.

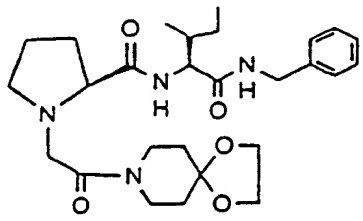
mp = 76-80 °C
R_f (100% ethyl acetate) = 0.04
Mass Spectrum (EI) m/e (rel intensity) 376 (20, M+H), 307 (38), 154 (100), 136 (82).

Example 66



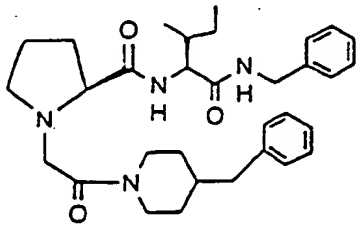
L-Isoleucine, N-[1-[2-[N-(Piperidine-3-Carboxylic Acid Ethyl Ester)]-2-Oxoethyl]-L-Prolyl] Benzylamide. A -5 °C solution of L-isoleucine, N-[1-(carboxymethyl)-L-prolyl] benzylamide (266 mg, 0.71 mmol, 1.0 eq), N-ethylmorpholine (135 uL, 1.06 mmol, 1.5 eq) in acetonitrile (5.0 mL) was treated with isobutyl chloroformate (101 uL, 0.78 mmol, 1.1 eq) followed by ethyl nipecotate (220 uL, 1.40 mmol, 2.0 eq). Purification by flash chromatography provided 150 mg (41%) of the title compound as a colorless oil. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (100% ethyl acetate) = 0.22

Example 67



L-Isoleucine, N-[1-(2-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide. A-5°C solution of L-isoleucine, N-[1-(carboxymethyl)-L-prolyl] benzylamide (254 mg, 0.67 mmol, 1.0 eq), N-methylmorpholine (96 uL, 0.88 mmol, 1.30 eq) in acetonitrile (7 mL) was treated with isobutyl chloroformate (96 uL, 0.74 mmol, 1.1 eq) followed by 1,4-dioxa-8-aza-spiro[4.5] decane (0.193 g, 1.35 mmol, 2.0 eq). Purification by flash chromatography provided 280 mg (83%) of the title compound as a colorless oil. The 300 MHz, ^{1}H NMR and mass spectrum analysis of this compound was consistent with the structure.
R_f (100% ethyl acetate) = 0.13
R_f (20% MeOH in ethyl acetate) = 0.68
Mass Spectrum (+EI) m/e (rel intensity) 500 (10,M+), 330 (12), 253 (100), 142 (18).

Example 68



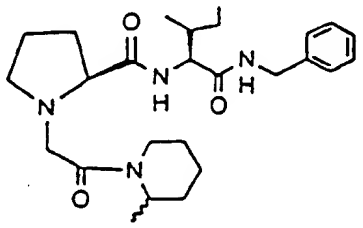
L-Isoleucine, N-[1-[2-(N-(4-Benzylpiperidyl))-2-Oxoethyl]-L-Prolyl] Benzylamide. A -5 °C solution of L-isoleu-

cine, N-[1-(carboxymethyl)-L-prolyl] benzylamide (321 mg, 0.85 mmol, 1.0 eq), N-methylmorpholine (122 uL, 1.11 mmol, 1.30 eq) in acetonitrile (8 mL) was treated with isobutyl chloroformate (127 uL, 0.98 mmol, 1.15 eq) followed by 4-benzylpiperidine (0.299 g, 1.71 mmol, 2.0 eq). Purification by flash chromatography provided 401 mg (88%) of the title compound as a colorless oil. The 300 MHz, ^{1}H NMR and mass spectrum analysis of this compound was consistent with the structure.

R_f (100% ethyl acetate) = 0.29: R_f (20% MeOH in ethyl acetate) = 0.69

Mass Spectrum (+CI) m/e (rel intensity) 532 (70,M+), 425 (30), 357 (22), 330 (100).

Example 69



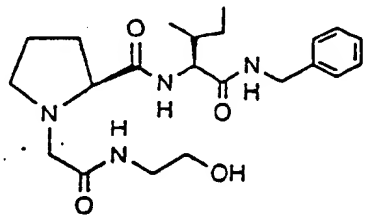
L-Isoleucine, N-[1-[2-(2-Methylpiperidine)-2-Oxoethyl]-L-Prolyl] Benzylamide. A -5 °C solution of L-isoleucine, N-[1-(carboxymethyl)-L-prolyl] benzylamide (202 mg, 0.53 mmol, 1.0 eq), N-ethylmorpholine (82 uL, 0.64 mmol, 1.20 eq) in acetonitrile (8 mL) was treated with isobutyl chloroformate (80 uL, 0.62 mmol, 1.15 eq) followed by 2-methylpiperidine (0.106 g, 1.07 mmol, 2.0 eq). The solution was warmed to 22 °C, concentrated to a residue, and purified by flash chromatography to provide 80 mg (32%) of the title compound as a colorless oil. The 300 MHz, ^{1}H NMR and mass spectrum analysis of this compound was consistent with the structure.

R_f (100% ethyl acetate) = 0.26

R_f (20% MeOH in ethyl acetate) = 0.61

Mass Spectrum (+EI) m/e (rel intensity) 456 (10,M+), 330 (14), 209 (100), 82 (82)

Example 70

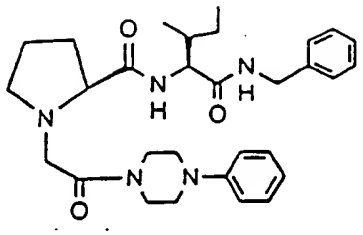


L-Isoleucine, N-[1-(2-(2-Hydroxyethylamine)-2-Oxoethyl)-L-Prolyl] Benzylamide. A -5 °C solution of L-isoleucine, N-[1-(carboxymethyl)-L-prolyl] benzylamide (0.215 g, 0.58 mmol, 1.0 eq), and triethylamine (96 uL, 70 mg, 0.64 mmol, 1.20 eq), in acetonitrile (10 mL) was treated with isobutyl chloroformate (83 uL, 86 mg, 0.63 mmol, 1.1 eq) followed by 2-aminoethanol (69 uL, 70 mg, 1.15 mmol, 2.0 eq). Workup as above provided 127 mg (53 %) of the title compound. The 300 MHz, ^{1}H NMR and mass spectrum analysis of this compound was consistent with the structure.

R_f(100% ethyl acetate) = 0.05

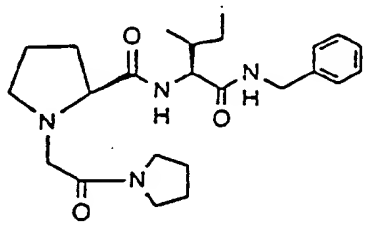
Mass Spectrum (+EI) m/e (rel intensity) 418 (10, M+), 330 (10), 171 (100), 153 (30).

Example 71



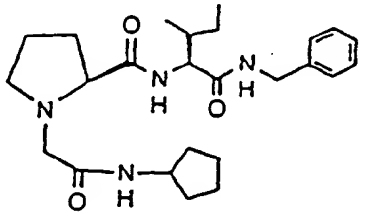
L-Isoleucine, N-[1-[2-(4 Phenylpiperazine)-2-Oxoethyl]-L-Prolyl] Benzylamide. A -5 °C solution of L-isoleucine, N-[1-(carboxymethyl)-L-prolyl] benzylamide (0.214 g, 0.58 mmol, 1.0 eq), and triethylamine (96 uL, 70 mg, 0.64 mmol, 1.20 eq), in acetonitrile (6 mL) was treated with isobutyl chloroformate (83 uL, 86 mg, 0.63 mmol, 1.1 eq) followed by 4-phenylpiperazine (170 uL, 186 mg, 1.15 mmol, 2.0 eq). Workup as above provided 170 mg (57 %) of the title compound. The 300 MHz, ^{1}H NMR and mass spectrum analysis of this compound was consistent with the structure.
R_f(100% ethyl acetate) = 0.18
Mass Spectrum (+EI) m/e (rel intensity) 519 (30, M+), 330 (22), 272 (100), 161 (20), 136 (25).

Example 72



L-Isoleucine, N-[1-[2-(1-Pyrrolidine)-2-Oxoethyl]-L-Prolyl] Benzylamide. A-5 °C solution of L-isoleucine, N-[1-(carboxymethyl)-L-prolyl] benzylamide (0.212 g, 0.56 mmol, 1.0 eq), and triethylamine (96 uL, 65 mg, 0.65 mmol, 1.15 eq), in acetonitrile (10 mL) was treated with isobutyl chloroformate (77 uL, 80 mg, 0.59 mmol, 1.05 eq) followed by pyrrolidine (94 uL, 80 mg, 1.13 mmol, 2.0 eq). Workup as above provided 205 mg (85 %) of the title compound. The 300 MHz, ^{1}H NMR and mass spectrum analysis of this compound was consistent with the structure.
R_f(100% ethyl acetate) = 0.14
Mass Spectrum (+EI) m/e (rel intensity) 428 (13, M+), 330 (10), 208 (10), 181 (100), 82 (85).

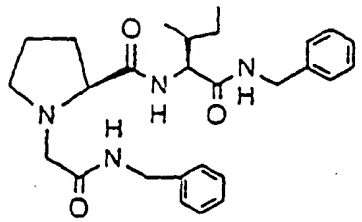
Example 73



L-Isoleucine, N-[1-[2-(N-Cyclopentylamino)-2-Oxoethyl]-L-Prolyl] Benzylamide. A -5 °C solution of L-isoleucine, N-[1-(carboxymethyl)-L-prolyl] benzylamide (0.212 g, 0.56 mmol, 1.0 eq), and triethylamine (96 uL, 65 mg, 0.65 mmol, 1.15 eq), in acetonitrile (10 mL) was treated with isobutyl chloroformate (77 uL, 86 mg, 0.59 mmol, 1.05 eq) followed by cyclopentylamine (111 uL, 96 mg, 1.13 mmol, 2.0 eq). Workup as above provided 198 mg (79 %) of the title compound. Th 300 MHz, ^{1}H NMR and mass spectrum analysis of this compound was consistent with th structure.
R_f(100% thyl ac tat) = 0.22
R_f(20% MeOH in ethyl acetate) = 0.55

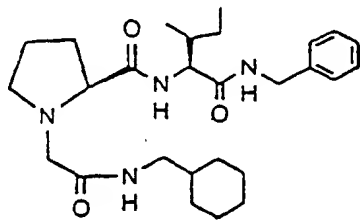
Mass Spectrum (+EI) m/e (rel intensity) 442 (28, M+), 375 (11), 330 (35), 297 (28), 212 (100).

Example 74



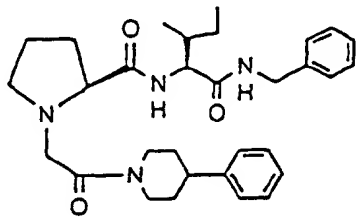
L-Isoleucine, N-[1-[2-(N-(Phenylmethylamino))-2-Oxoethyl]-L-Prolyl] Benzylamide. A -5 °C solution of L-isoleucine, N-[1-(carboxymethyl)-L-prolyl] benzylamide (0.218 g, 0.58 mmol, 1.0 eq), and triethylamine (89 uL, 64 mg, 0.64 mmol, 1.10 eq), in acetonitrile (10 mL) was treated with isobutyl chloroformate (79 uL, 83 mg, 0.61 mmol, 1.05 eq) followed by benzylamine (82 uL, 80 mg, 0.75 mmol, 1.3 eq). After the addition was complete, the flask was removed from the cold bath and the solution was stirred at 22 °C for 3 hrs. Workup as above provide 227 mg (84%) of the title compound as a white solid. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
mp = 76-80 °C
R_f(100% ethyl acetate) = 0.25

Example 75



L-Isoleucine, N-[1-[2-(N-(Cyclohexylmethylamino))-2-Oxoethyl]-L-Prolyl] Benzylamide. Using the procedure described previously, a solution of L-isoleucine, N-[1-(carboxymethyl)-L-prolyl] benzylamide (0.220 g, 0.58 mmol, 1.0 eq), and triethylamine (89 uL, 64 mg, 0.64 mmol, 1.10 eq), in acetonitrile (10 mL) was treated with isobutyl chloroformate (79 uL, 83 mg, 0.61 mmol, 1.05 eq) followed by cyclohexylmethylamine (99 uL, 86 mg, 0.75 mmol, 1.30 eq). Workup as above provided 201 mg (73 %) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f(100% ethyl acetate) = 0.23
R_f(20% MeOH in ethyl acetate) = 0.64

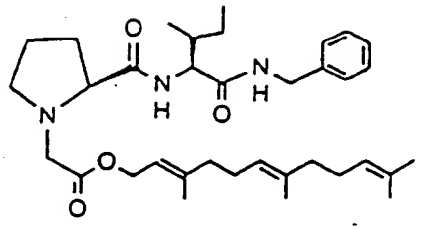
Example 76



L-Isoleucine, N-[1-(2-(4-Phenylpiperidyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described abov , a solution of L-isoleucine, N-[1-(carboxymethyl)-L-prolyl] benzylamide (0.124 g, 0.33 mmol, 1.0 eq), and N-m thylmorpholine (43 uL, 40 mg, 0.40 mmol, 1.20 eq), in acetonitril (3 mL) was treated with isobutyl chloroformate (45 uL, 47 mg, 0.35 mmol, 1.05 eq) followed by 4-phenylpiperidine (69 mg, 0.43 mmol, 1.3 eq). Workup as abov

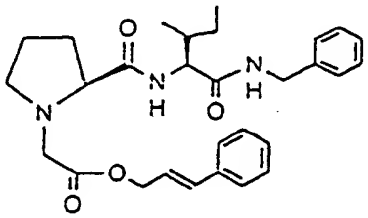
provided 101 mg (59 %) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structur .
R_f(100% ethyl acetate) = 0.18

Example 77



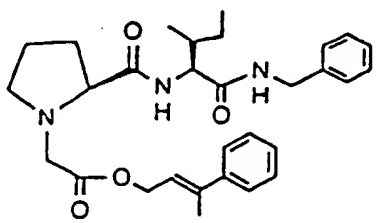
L-Isoleucine, N-[1-(2-[1-(3,7,11-Trimethyldodeca-2,6,10-trien-1-ol)]-2-Oxoethyl)-L-Proline] Benzylamide. A solution of L-isoleucine, N-[1-(carboxymethyl)-L-prolyl] benzylamide (67 mg, 0.18 mmol), 4-N,N-dimethylaminopyridine (6.1 mg, 0.05 mmol, 0.3 eq), 1,3-dicyclohexylcarbodiimide (64 mg, 0.31 mmol, 1.8 eq) in dichloromethane (2.0 mL) was treated with trans,trans farnesol (55 uL, 0.22 mmol, 1.2 eq). After TLC indicated the reaction was complete, the mixture was purified by HPLC to provide 27 mg (26%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (50% ethyl acetate in dichloromethane) = 0.50
HRMS calcd for $(M+H)^+$ [$(C_{35}H_{53}N_3O_4 + H)^+$] ion 580.8365; found 550.4117

Example 78



L-Isoleucine, N-[1-(2-(3-Phenyl-2-Propen-1-Oxy)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described previously, a solution of L-isoleucine, N-[1-(carboxymethyl)-L-prolyl] benzylamide (65 mg, 0.17 mmol), 4-N, N-dimethylaminopyridine (12.5 mg, 0.10 mmol, 0.6 eq), 1,3-dicyclohexylcarbodiimide (64 mg, 0.31 mmol, 1.8 eq) in dichloromethane (5.0 mL) was treated with trans cinnamyl alcohol (29 uL, 0.22 mmol, 1.3 eq). After TLC indicated the reaction was complete, the mixture was purified by HPLC to provide 32 mg (38%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (50% ethyl acetate in dichloromethane) = 0.47
HRMS calcd for $(M+H)^+$ [$(C_{29}H_{38}N_3O_4 + H)^+$] ion 492.6424; found 492.2864

Example 79



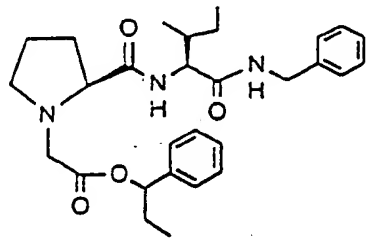
L-Isoleucine, N-[1-(2-(3-Phenyl-3-Methyl-2-Propen-1-Oxy)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the

procedure described previously, a solution of L-isoleucine, N-[1-(carboxymethyl)-L-prolyl] benzylamide (56 mg, 0.15 mmol), 4-N,N-dimethylaminopyridine (3.6 mg, 0.03 mmol, 0.2 eq), 1,3-dicyclohexylcarbodiimide (54 mg, 0.26 mmol, 1.7 eq) in dichloromethane (5.0 mL) was treated with trans 2-methyl-3-phenyl-2-propen-1-ol (28 uL, 0.19 mmol, 1.3 eq). After TLC indicated the reaction was complete, the mixture was purified by HPLC to provide 32 mg (42%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.

R_f (50% ethyl acetate in dichloromethane) = 0.52

HRMS calcd for $(M+H)^+$ $[(C_{30}H_{40}N_3O_4 + H)^+]$ ion 506.6695; found 506.3021

Example 80

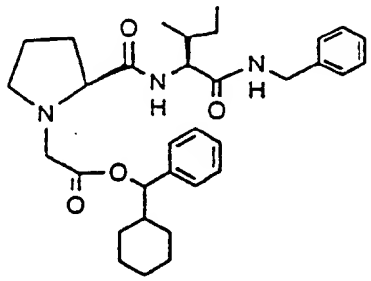


L-Isoleucine, N-[1-(2-(1-Phenylpropoxy)-2-Oxoethyl)-L-Prolyl], Benzylamide. A solution of L-isoleucine, N-[1-(carboxymethyl)-L-prolyl] benzylamide (59 mg, 0.16 mmol), 4-N,N-dimethylaminopyridine (7.9 mg, 0.06 mmol, 0.4 eq), 1,3-dicyclohexylcarbodiimide (49 mg, 0.23 mmol, 1.5 eq) in dichloromethane (5.0 mL) was treated with (+/-) 1-phenyl-1-propanol (28 uL, 0.20 mmol, 1.3 eq). After TLC indicated the reaction was complete, the mixture was purified by HPLC to provide 32 mg (41%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.

R_f (50% ethyl acetate in dichloromethane) = 0.51

HRMS calcd for $(M+H)^+$ $[(C_{29}H_{40}N_3O_4 + H)^+]$ ion 494.6584; found 494.3021

Example 81

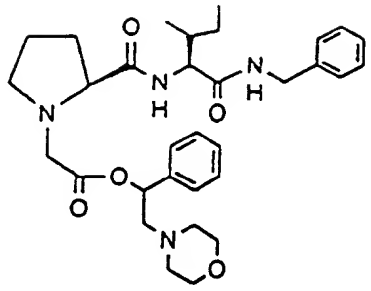


L-Isoleucine, N-[1-(2-(1-Phenyl-1-Cyclohexylmethoxy)-2-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described previously, a solution of L-isoleucine, N-[1-(carboxymethyl)-L-prolyl] benzylamide (71 mg, 0.19 mmol), 4-N,N-dimethylaminopyridine (7.5 mg, 0.06 mmol, 0.3 eq), 1,3-dicyclohexylcarbodiimide (64 mg, 0.31 mmol, 1.6 eq) in dichloromethane (5.0 mL) was treated with (+/-) cyclohexylphenylcarbinol (45 mg, 0.24 mmol, 1.3 eq). After TLC indicated the reaction was complete, the mixture was purified by HPLC to provide 27 mg (26%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.

R_f (50% ethyl acetate in dichloromethane) = 0.51

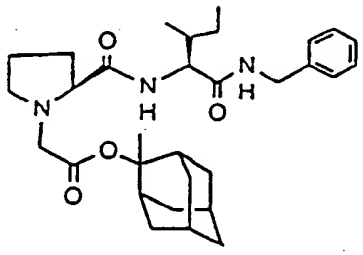
HRMS calcd for $(M+H)^+$ $[(C_{33}H_{46}N_3O_3 + H)^+]$ ion 548.7506; found 548.3491

Exampl 82



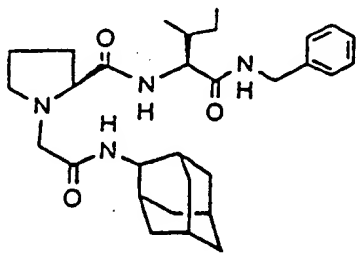
L-Isoleucine, N-[1-(2-(1-Phenyl-2-(4-Morpholino)Ethoxy)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described previously, a solution of L-isoleucine, N-[1-(carboxymethyl)-L-prolyl] benzylamide (58 mg, 0.15 mmol), 4-N,N-dimethylaminopyridine (13.2 mg, 0.10 mmol, 0.7 eq), 1,3-dicyclohexylcarbodiimide (57 mg, 0.27 mmol, 1.8 eq) in dichloromethane (5.0 mL) was treated with (+/-) alpha-phenyl-4-morpholinoethanol (60 mg, 0.29 mmol, 1.9 eq). After TLC indicated the reaction was complete, the mixture was purified by HPLC to provide 20 mg (22%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (50% ethyl acetate in dichloromethane) = 0.32

Example 83



L-Isoleucine, N-[1-(2-(2-Oxy-2-Methyladamant-2-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described previously, a solution of L-isoleucine, N-[1-(carboxymethyl)-L-prolyl] benzylamide (61 mg, 0.16 mmol), 4-N,N-dimethylaminopyridine (26 mg, 0.21 mmol, 1.3 eq), 1,3-dicyclohexylcarbodiimide (51 mg, 0.25 mmol, 1.5 eq) in dichloromethane (3.0 mL) was treated with 2-methyl-2-adamantanol (33 mg, 0.21 mmol, 1.3 eq). After TLC indicated the reaction was complete, the mixture was purified by HPLC to provide 20 mg (23%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (50% ethyl acetate in dichloromethane) = 0.45
HRMS calcd for (M+H)$^+$ [($C_{31}H_{46}N_3O_3$ + H)$^+$] ion 524.7284; found 524.3491

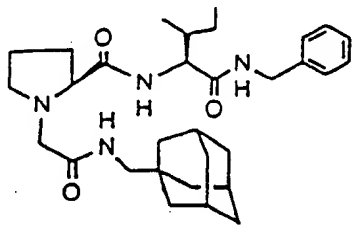
Example 84



L-Isoleucine, N-[1-(Adamantan-2-ylcarbamoylmethyl)-L-Prolyl] Benzylamide. Using th procedure described previously, a solution of L-isoleucine, N-[1-(carboxymethyl)-L-prolyl] benzylamid (113 mg, 0.30 mmol), triethylamine

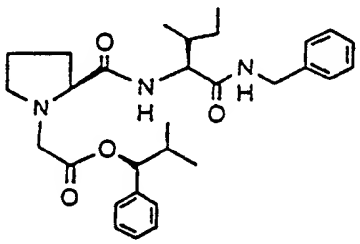
(168 uL, 1.20 mmol, 4 eq) in acetonitrile (1.5 mL), was cooled to 0 °C and treated with isobutyl chloroformate (43 uL, 0.33 mmol, 1.1 eq) followed by the hydrochloride salt of 2-adamantylamine (113.2 mg, 0.60 mmol, 2 eq). After TLC indicated the reaction was complete, the mixture was purified by HPLC to provide 10 mg (6.5%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (100% ethyl acetate) = 0.26

Example 85



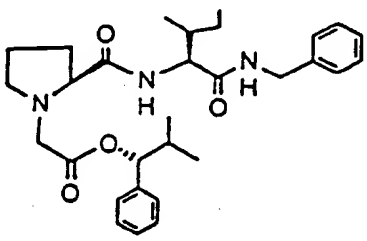
L-Isoleucine, N-[1-(Adamant-1-ylmethylcarbamoylmethyl)-L-Prolyl] Benzylamide. Using the procedure described previously, a solution of L-isoleucine, N-[1-(carboxymethyl)-L-prolyl] benzylamide (106 mg, 0.28 mmol), triethylamine (158 uL, 1.13 mmol, 4 eq) in acetonitrile (1.5 mL, was cooled to 0 °C and treated with isobutyl chloroformate (40.5 uL, 0.31 mmol, 1.1 eq) followed by 1-adamantanemethylamine (100 uL, 0.57 mmol, 2 eq). After TLC indicated the reaction was complete, the mixture was purified by HPLC to provide 15 mg (10%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (100% ethyl acetate) = 0.25
HRMS calcd for $(M+H)^+$ [$(C_{31}H_{47}N_4O_3 + H)^+$] ion 523.7436; found 523.3651

Example 86



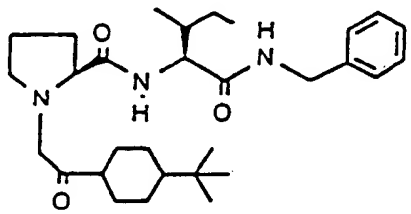
L-Isoleucine, N-[1-(2-(2-Methyl-1-(S)-Phenyl-1-Propoxy)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described previously, a solution of L-isoleucine, N-[1-(carboxymethyl)-L-prolyl] benzylamide (298 mg, 0.73 mmol), 4-N,N-dimethylaminopyridine (95 mg, 0.77 mmol, 1.2 eq), 1,3-dicyclohexylcarbodiimide (243 mg, 1.18 mmol, 1.8 eq) in dichloromethane (10 mL) was treated with (S)-2-methyl-1-phenyl-1-propanol (100 mg, 0.64 mmol, 1.3 eq). After TLC indicated the reaction was complete, the mixture was purified by HPLC to provide 104 mg (32%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (50% ethyl acetate in dichloromethane) = 0.57

Example 87



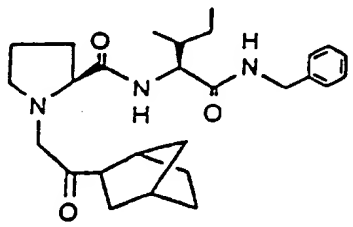
L-Isoleucine, N-[1-(2-(2-Methyl-1-(R)-Phenyl-1-Propoxy)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described previously, a solution of L-isoleucine, N-[1-(carboxymethyl)-L-prolyl] benzylamid (298 mg, 0.73 mmol), 4-N,N-dimethylaminopyridine (100 mg, 0.82 mmol, 1.3 eq), 1,3-dicyclohexylcarbodiimide (242 mg, 1.17 mmol, 1.8 eq) in dichloromethane (10 mL) was treated with (R)-2-methyl-1-phenyl1-propanol (100 mg, 0.64 mmol, 1.3 eq). After TLC indicated the reaction was complete, the mixture was purified by HPLC to provide 96.2 mg (30%) of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f (50% ethyl acetate in dichloromethane) = 0.57

Example 88



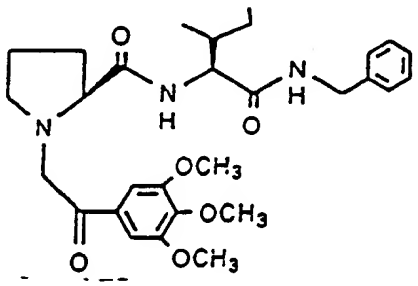
L-Isoleucine, N-[1-(2-(4-tert-Butylcyclohexyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (200 mg, 0.63 mmol) with 4-(t-butyl)cyclohexyl α-chloromethyl ketone (164 mg, 0.76 mmol, 1.2 eq; prepared from 4-tert-butylcyclohexane-carboxylic acid), provided 160 mg of the title compound as a white foam. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f = 0.45 (50% EtOAc in CH_2Cl_2).
LSIMS = 498 (mass calculated for $C_{30}H_{47}N_3O_3$ = 497.73).

Example 89



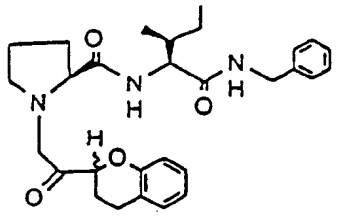
L-Isoleucine, N-[1-(2-Bicyclo[2.2.1]hept-2-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (100 mg, 0.32 mmol) with 2-norbornyl α-chloromethyl ketone (82 mg, 0.48 mmol, 1.5 eq; prepared from 2-norbornanecarboxylic acid) provided 69 mg of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f = 0.28 (70% EtOAc in hexane).
LSIMS = 454 (mass calculated for $C_{27}H_{39}N_3O_3$ = 453.63).

Example 90



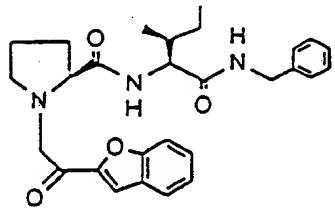
L-Isoleucine, N-[1-(2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (100 mg, 0.32 mmol) with 3,4,5-trimethoxyphenyl α-chloromethyl ketone (116 mg, 0.47 mmol, 1.5 eq; prepared from 3,4,5-trimethoxybenzoic acid) provided 190 mg of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f = 0.33 (50% EtOAc in CH_2Cl_2).

Example 91



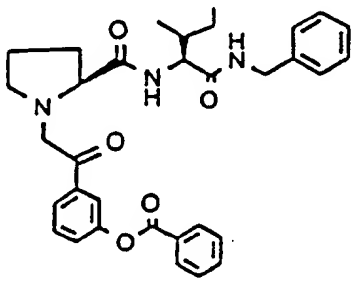
L-Isoleucine, N-[1-(2-(Chroman-2-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide Hydrochloride Salt. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (200 mg, 0.63 mmol) with benzopyranyl α-chloromethyl ketone (266 mg, 1.26 mmol, 2 eq; prepared from 3,4-dihydro-2H-1-benzopyran-2-carboxylic acid) provided the amine which was treated with HCl in ether to provide 200 mg of the hydrochloride salt of the title compound as a mixture of diastereomers. The 300 MHz, ^{1}H NMR analysis of this compoud was consistent with the structure.
R_f = 0.38 (for free base: 80% EtOAc in hexane).
LSIMS [M-HCl] = 491 (mass calculated for $C_{29}H_{37}N_3O_4$ + HCl = 528.09).

Example 92



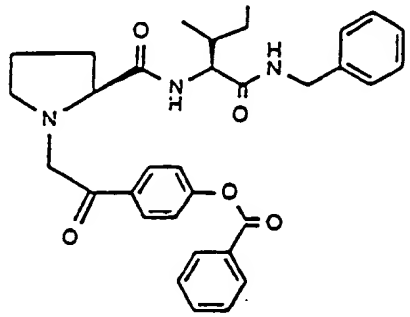
L-Isoleucine, N-[1-(2-(Benzofuran-2-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide Hydrochloride Salt. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (200 mg, 0.63 mmol) with benzofuranyl α-chloromethyl ketone (246 mg, 1.26 mmol, 2 eq; prepared from 2-benzofurancarboxylic acid) provided the amine which was treated with HCl in ether to provide 200 mg of the hydrochloride salt of the title compound as a solid. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f = 0.13 (for free base: 50% EtOAc in hexane).
LSIMS [M-HCl] = 476 (mass calculated for $C_{28}H_{33}N_3O_4$ + HCl = 512.05).

Example 93



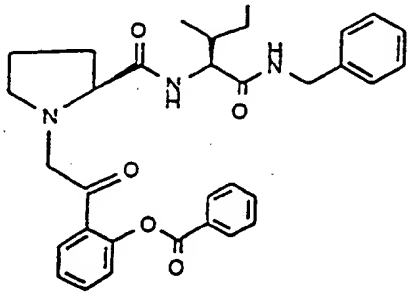
L-Isoleucine, N-[1-(2-(3-Benzoyloxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (200 mg, 0.63 mmol) with 3'-benzoyloxy-2-bromoacetophenone (302 mg, 0.95 mmol, 1.5 eq) provided 57 mg of the title compound as a solid. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
LIMS = 556 (mass calculated for $C_{33}H_{37}N_3O_5$ = 555.68).

Example 94



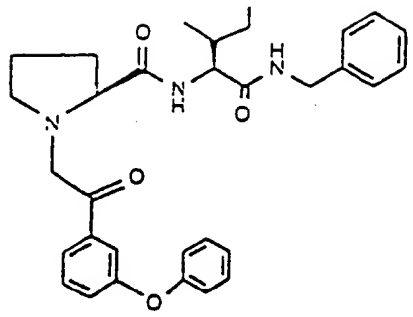
L-Isoleucine, N-[1-(2-(4-Benzoyloxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (200 mg, 0.63 mmol) with 4'-benzoyloxy-2-bromoacetophenone (302 mg, 0.95 mmol, 1.5 eq) provided 171 mg of the title compound as a foam. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
LSIMS = 556 (mass calculated for $C_{33}H_{37}N_3O_5$ = 555.68).

Example 95



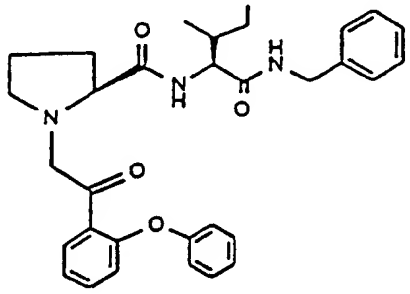
L-Isoleucine, N-[1-(2-(2-Benzoyloxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (200 mg, 0.63 mmol) with 2'-benzoyloxy-2-bromoacetophenone (302 mg, 0.95 mmol, 1.5 eq) provided 120 mg of the title compound as a foam. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
LSIMS = 556 (mass calculated for $C_{33}H_{37}N_3O_5$ = 555.68).

Example 96



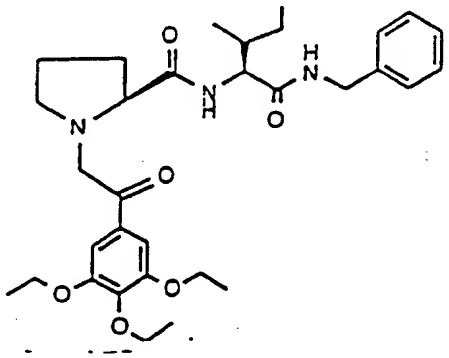
L-Isoleucine, N-[1-(2-(3-Phenoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (200 mg, 0.63 mmol) with 3'-phenoxy-2-chloroacetophenone (233 mg, 0.95 mmol, 1.5 eq; prepared from 3-phenoxybenzoic acid) provided 80 mg of the title compound as a foam. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f = 0.26 (70% EtOAc in hexane).
LSIMS = 528 (mass calculated for $C_{32}H_{37}N_3O_4$ = 527.67).

Example 97



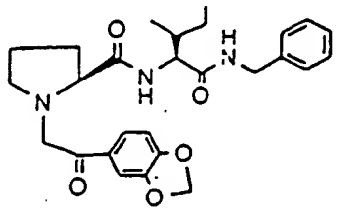
L-Isoleucine, N-[1-(2-(2-Phenoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (200 mg, 0.63 mmol) with 2'-phenoxy-2-chloroacetophenone (233 mg, 0.95 mmol, 1.5 eq; prepared from 2-phenoxybenzoic acid) provided 40 mg of the title compound as a foam. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f = 0.31 (70% EtOAc in hexane).
LSIMS = 528 (mass calculated for $C_{32}H_{37}N_3O_4$ = 527.67).

Example 98



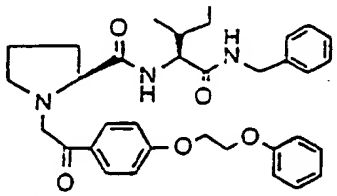
L-Isoleucine, N-[1-(2-(3,4,5-Triethoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (200 mg, 0.63 mmol) with 3,4,5-triethoxyphenyl α-chloromethyl ketone (271 mg, 0.95 mmol, 1.5 eq; prepared from 3,4,5-triethoxybenzoic acid), provided 45 mg of the title compound as a foam. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f = 0.19 (70% EtOAc in hexane).
LSIMS = 568 (mass calculated for $C_{32}H_{45}N_3O_6$ = 567.73).

Example 99



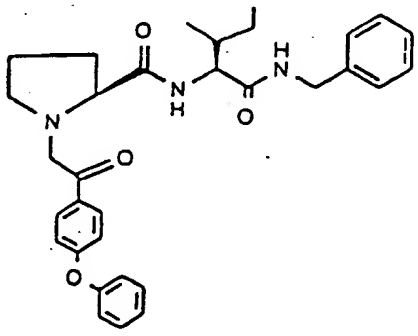
L-Isoleucine, N-[1-(2-(Benzo[1,3]dioxol-5-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (200 mg, 0.63 mmol) with piperonyl α-chloromethyl ketone (188 mg, 0.95 mmol, 1.5 eq; prepared from piperonylic acid), provided 84 mg of the title compound as a foam. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f = 0.24 (70% EtOAc in hexane).
LSIMS = 480 (mass calculated for $C_{27}H_{33}N_3O_5$ = 479.58).

Example 100



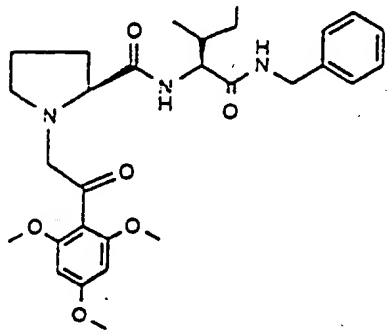
L-Isoleucine, N-[1-{2-Oxo-2-[4-(2-Phenoxyethoxy)-Phenyl]-Ethyl}-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (200 mg, 0.63 mmol) with 4'-phenoxyethoxy-2-chloroacetophenone, (275 mg, 0.95 mmol, 1.5 eq; prepared from 4-(2-phenoxyethoxy)benzoic acid), provided 80 mg of the title compound as a crystalline solid. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
LSIMS = 572 (mass calculated for $C_{34}H_{41}N_3O_6$ = 571.72).

Example 101



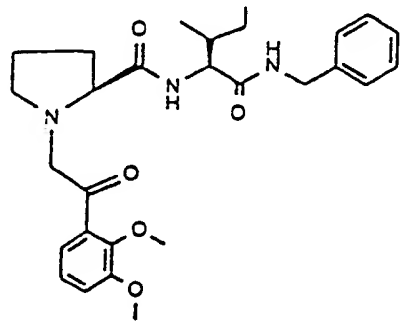
L-Isol ucine, N-[1-(2-(4-Phenoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in exampl 1e, treatment of L-proline-L-isoleucine benzylamide (200 mg, 0.63 mmol) with 4'-phenoxy-2-bromoacetophenone (275 mg, 0.95 mmol, 1.5 eq) provided 142 mg of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
LSIMS = 528 (mass calculated for $C_{32}H_{37}N_3O_4$ = 527.67).

Example 102



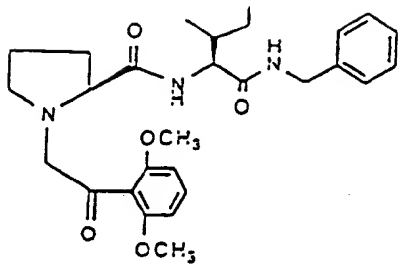
L-Isoleucine, N-[1-(2-(2,4,6-Trimethoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (200 mg, 0.63 mmol) with 2',4',6'-trimethoxyphenyl α-bromomethyl ketone (273 mg, 0.95 mmol, 1.5 eq) provided 88 mg of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
LSIMS = 526 (mass calculated for $C_{29}H_{39}N_3O_6$ = 525.65).

Example 103



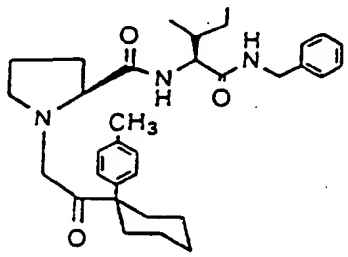
L-Isoleucine, N-[1-(2-(2,3-Dimethoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (200 mg, 0.63 mmol) with 2',3'-dimethoxyphenyl α-chloromethyl ketone (190 mg, 0.88 mmol, 1.4 eq; prepared from 2,3-dimethoxybenzoic acid) provided 34 mg of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
LSIMS = 496 (mass calculated for $C_{28}H_{37}N_3O_5$ = 495.62).

Example 104



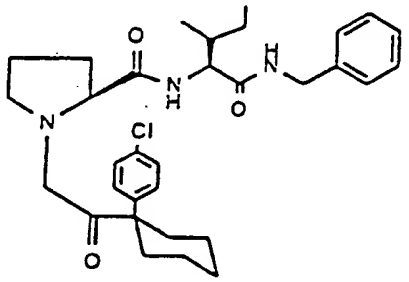
L-Isoleucine, N-[1-(2-(2,6-Dimethoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (200 mg, 0.63 mmol) with 2',6'-dimethoxyphenyl α-bromomethyl ketone (326 mg, 1.26 mmol, 2.0 eq) provided 80 mg of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
LSIMS = 496 (mass calculated for $C_{28}H_{37}N_3O_5$ = 495.62).

Example 105



L-Isoleucine, N-[1-(2-(1-(4-Methylphenyl)cyclohexyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (200 mg, 0.63 mmol) with 1-(4-methylphenyl)cyclohexyl α-chloromethyl ketone (237 mg, 1.26 mmol, 2.0 eq; prepared from 1-(4-methylphenyl)-1-cyclohexanecarboxylic acid) provided 30 mg of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
LSIMS = 532 (mass calculated for $C_{33}H_{45}N_3O_3$ = 531.74).

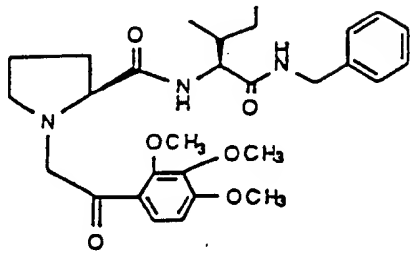
Example 106



L-Isoleucine, N-[1-(2-(1-(4-Chlorophenyl)cyclohexyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (200 mg, 0.63 mmol) with 1-(4-chloroph nyl)cyclohexyl α-chl romethyl ketone (342 mg, 1.26 mmol, 2.0 eq; prepared from 1-(4-chloroph nyl)-1-cyclohexanecarboxylic acid) provided 30 mg of the titl compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with th structure.

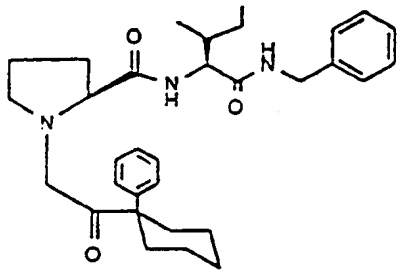
LSIMS = 552 (mass calculated for $C_{32}H_{42}ClN_3O_3$ = 552.16).

Example 107



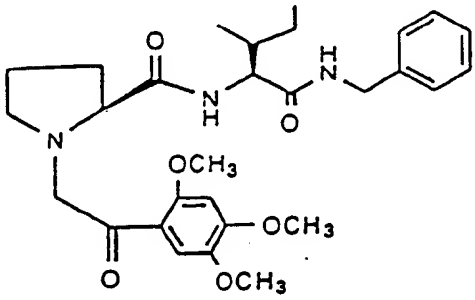
L-Isoleucine, N-[1-(2-(2,3,4-Trimethoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (200 mg, 0.63 mmol) with 2,3,4-trimethoxyphenyl α-chloromethyl ketone (273 mg, 0.95 mmol, 1.5 eq) provided 100 mg of the title compound. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
LSIMS = 526 (mass calculated for $C_{29}H_{39}N_3O_6$ = 525.65).

Example 108



L-Isoleucine, N-[1-(2-(1-Phenylcyclohexyl)-2-Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure described in example 1e, treatment of L-proline-L-isoleucine benzylamide (200 mg, 0.63 mmol) with 1-phenylcyclohexyl α-chloromethyl ketone (224 mg, 0.95 mmol, 1.5 eq; prepared from 1-phenyl-1-cyclohexanecarboxylic acid) provided 40 mg of the title compound. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
LSIMS = 518 (mass calculated for $C_{32}H_{43}N_3O_3$ = 517.72).

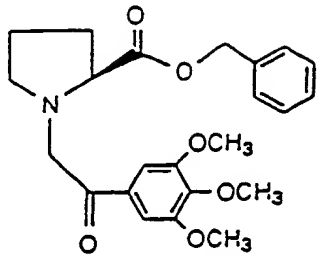
Example 109



L-Isoleucine, N-[1-(2-(2,4,5-Trimethoxyphenyl)(-2-(Oxoethyl)-L-Prolyl] Benzylamide. Using the procedure describ d in example 1e, treatment of L-prolin -L-isoleucine benzylamide (200 mg, 0.63 mmol) with 2',4',5'-trimethoxyph nyl α-bromomethyl ketone (274 mg, 0.95 mmol, 1.5 eq) provided 40 mg of the title compound. Th 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.

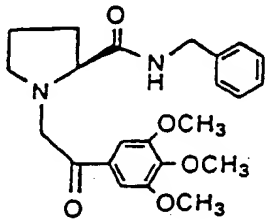
LSIMS = 526 (mass calculated for $C_{29}H_{39}N_3O_6$ = 525.65).

Example 110 (Not within the scope of the claims)



1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] L-Proline Benzyl Ester Hydrochloride. Using the procedure described in example 1e, treatment of L-proline benzyl ester hydrochloride (1.00 g, 4.14 mmol) and 3,4,5-trimethoxyphenyl α-bromomethyl ketone (2.4 g, 8.27 mmol) provided the amine (Rf = 0.37: 50% EtOAc in hexane). The amine intermediate was treated with HCl in ether and dried in vacuo to provided 1.58 g of the title compound as a solid. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.

Example 111

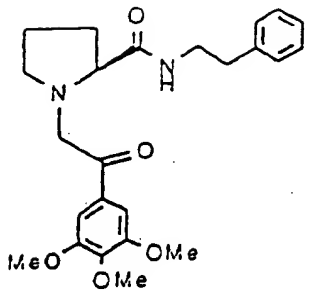


L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] Benzylamide Hydrochloride.

a) 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] L-Proline Hydrochloride. The hydrochloride salt of 1-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl] L-proline benzyl ester (1.53 g), was dissoved in ethanol (100 mL) and treated with 10% palladium on carbon (150 mg). The flask was purged with argon, purged with hydrogen and left to stir under hydrogen atmosphere (1 atm) until the reaction appeared complete by TLC. The catalyst was removed by filtration through Celite and solvent removed in vacuo to provide 1.15 g of the title compound as a solid. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.

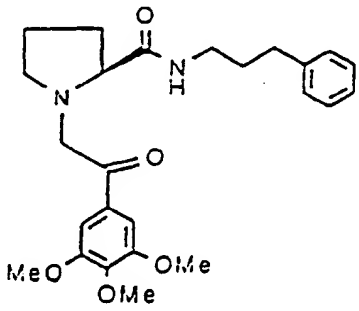
b) L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] Benzylamide Hydrochloride. To an oven-dried round bottomed flask was added N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-proline hydrochloride, (300 mg, 0.83 mmol, 1.0 eq), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (369 mg, 0.83 mmol, 1.0 eq.) and anhydrous tetrahydrofuran (10 mL). The slurry was cooled to 0 oC and treated with triethylamine (3.0 eq). After stirring 10 minutes at 0 °C, benzylamine (0.27 mL, 2.5 mmol, 3.0 eq) was added and the reaction mixture was allowed to warm to 22 °C over a one hour period. The solvent was removed in vacuo and the resulting residue was taken up in EtOAc (100 mL). The organic layer was washed with 5% citric acid (100 mL), sat. $NaHCO_3$ (100 mL), sat. aq. NaCl (100 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography, and treated with HCl in ether to provide 128 mg of the title compound as a powder. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
LSIMS [M-HCl] = 413 (mass calculated for $C_{23}H_{28}N_2O_5$ + HCl = 448.93).

Example 112



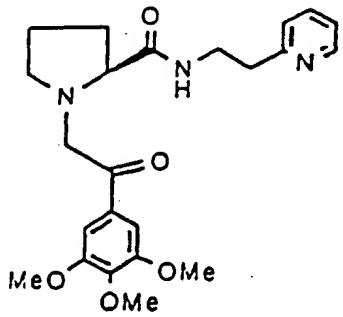
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-Phenethylamide Hydrochloride. Following the procedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-proline hydrochloride (300 mg, 0.53 mmol) and phenethylamine (0.31 mL, 2.5 mmol) provided, after treatment with HCl in Et_2O, 199 mg of the title compound as a powder. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
LSIMS [M-HCl]= 427 (mass calculated for $C_{24}H_{30}N_2O_5$ + HCl = 462.98).

Example 113



L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 3-Phenylpropylamide Hydrochloride. Following the procedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-proline hydrochloride (300 mg, 0.83 mmol) and 3-phenylpropylamine (0.36 mL, 2.5 mmol) provided, after treatment with HCl in Et_2O, 120 mg of the title compound as a powder. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
LSIMS [M-HCl]= 441 (mass calculated for $C_{25}H_{32}N_2O_5$ + HCl = 477.00).

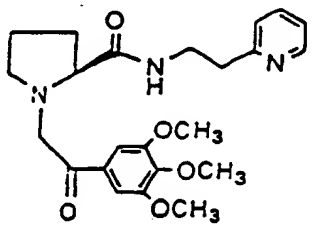
Example 114



L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 4-Phenylbutylamide Hydrochloride. Following the pro-

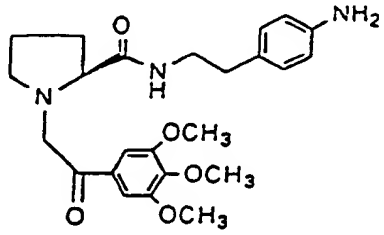
cedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-proline hydrochloride (300 mg, 0.83 mmol) and 4-phenylbutylamine (0.39 mL, 2.5 mmol) provided, after treatment with HCl in Et_2O, 170 mg of the title compound as a powder. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
LSIMS [M-HCl]= 455 (mass calculated for $C_{26}H_{34}N_2O_5$ + HCl = 491.03).

Example 115



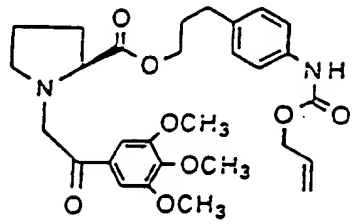
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-(Pyrid-2-yl)ethylamide Dihydrochloride. Following the procedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-proline hydrochloride (300 mg, 0.83 mmol) and 2(2-aminoethyl)pyridine (0.4 mL, 2.5 mmol) provided, after treatment with HCl in Et_2O, 193 mg of the title compound as a powder. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
LSIMS [M-2HCl]= 429 (mass calculated for $C_{23}H_{29}N_3O_5$ x 2HCl = 500.43).

Example 116



L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-(4-aminophenyl)ethylamide Dihydrochloride. Following the procedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-proline hydrochloride (300 mg, 0.83 mmol) and (4-aminophenyl)ethylamine (0.4 mL, 2.5 mmol) provided, after treatment with HCl in Et_2O, 102 mg of the title compound as a powder. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure. R_f = 0.27 (for free base: EtOAc)
LSIMS [M-2HCl]= 442 (mass calculated for $C_{24}H_{31}N_3O_5$x2HCl = 514.45)

Example 117 (Not within the scope of the claims)



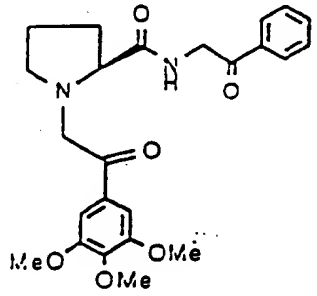
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 3-(4-[N-Carboallyloxy]aminophenyl)propyl Ester Hydrochloride.

a) 3-(4-Aminophenyl)propanol. To a round bottomed flask equipped with a magnetic stirrer was added 4-nitrocinnamyl alcohol (2.0 g, 11.16 mmol), 10% Pd on carbon (200 mg) and absolute ethanol (150 mL). The solution was purged with hydrogen and stirred at 22 °C under a hydrogen atmosphere. When TLC indicated the reaction was complete (4 h), the solution was purged with argon and filtered through Celite. The filtrat was concentrated *in vacuo* to provide 3-(4-aminophenyl)propanol, 1.72 g (>100%), as a viscous oil which solidified on standing. R_f = 0.17 (50% EtOAc in hexane).

b) 3-(4-(N-Carboallyloxy)-aminophenyl)propanol. To a round bottomed flask was added the 3-(4-aminophenyl) propanol (1.3 g, 8.6 mmol), pyridine (1.0 mL, 12 mmol) and dichloromethane (25 mL). The solution was cooled to 0 °C and treated with allyl chloroformate (1.0 mL, 9.4 mmol). After allowing to warm to 22 °C over 1 hour, the reaction mixture was diluted with dichloromethane and washed twice with 1N HCl, followed by sat. $NaHCO_3$, water and sat. aq. NaCl. The organic extract was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (50% EtOAc in hexane), provided 1.77 g (88%) of the title compound as a clear oil which solidified on standing. The ^1H NMR analysis of this compound was consistent with the structure.
R_f = 0.37 (60% EtOAc in hexane).

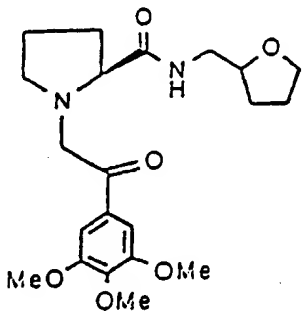
c) L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 3-(4-[N-Carboallyloxylaminophenyl)propyl Ester Hydrochloride. Following the procedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethy]-L-proline hydrochloride (300 mg, 0.83 mmol) and 3-(4-(N-carboallyloxy)aminophenyl)propanol (218 mg, 0.83 mmol) provided, after treatment with HCl in Et_2O, 65 mg of the title compound as a foam. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
LSIMS [M-HCl]= 542 (mass calculated for $C_{29}H_{36}N_2O_8$ + HCl = 577.08).

Example 118



L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-Phenyl-2-oxoethylamide. Following the procedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-proline hydrochloride (200 mg, 0.56 mmol) and 2-aminoacetophenone hydrochlride (286 mg, 1.67 mmol) provided 54 mg of the title compound as a powder. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
Rf = 0.46 (EtOAc)
LSIMS = 442 (mass calculated for $C_{24}H_{28}N_2O_6$ = 440.50).

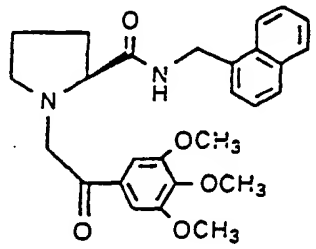
Example 119



L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] Tetrahydrofurfurylamide. Following the procedure d -

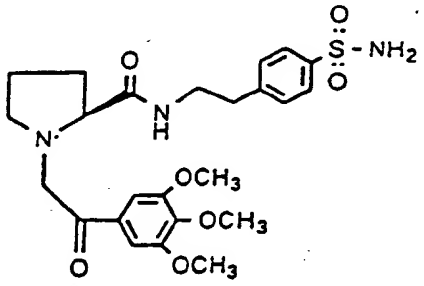
scribed in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-proline hydrochloride (200 mg, 0.56 mmol) and tetrahydrofurfurylamine (0.17 mL, 1.67 mmol) provided 104 mg of the title compound as a powder. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
Rf = 0.20 (EtOAc)
LSIMS = 407 (mass calculated for $C_{21}H_{30}N_2O_6$ = 406.48).

Example 120



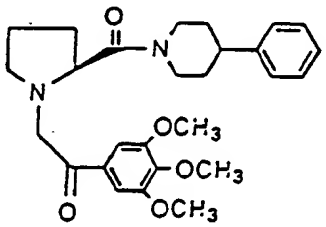
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] Naphthalen-1-ylmethylamide. Following the procedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-proline hydrochloride (300 mg, 0.83 mmol) and 1-naphthyl methylamine (0.37 mL, 2.5 mmol) provided 150 mg of the title compound as a powder. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
LSIMS = 463 (mass calculated for $C_{27}H_{30}N_2O_5$ = 462.55).

Example 121



L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-(4-Sulfamoylphenyl)ethylamide. Following the procedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-proline hydrochloride (300 mg, 0.83 mmol) and 4-(2-aminoethyl)benzene sulfonamide (334 mg, 1.67 mmol) provided 300 mg of the title compound as a powder. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
LSIMS = 506 (mass calculated for $C_{24}H_{31}N_3SO_7$ = 505.60).

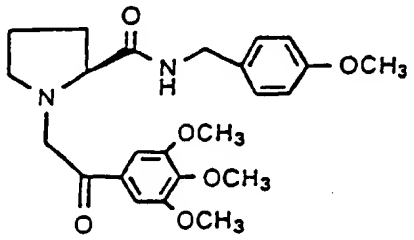
Example 122



L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 4-Phenylpiperidenylamide. Following the procedure

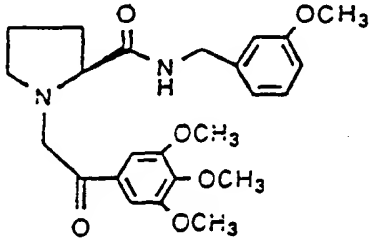
describ d in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-proline hydrochlorid (250 mg, 0.69 mmol) and 4-phenylpiperidine (336 mg, 2.1 mmol) provided 67 mg of the title compound as a foam. The 300 MHz, ^{1}H NMR analysis of this compound was consistent,vith the structure.
Rf = 0.22 (EtOAc)
LSIMS = 467 (mass calculated for $C_{27}H_{34}N_2O_5$ = 466.58).

Example 123



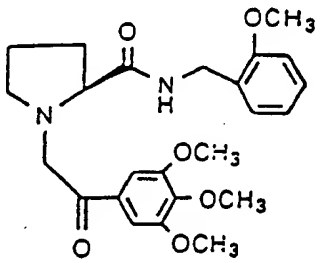
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 4Methoxybenzamide Hydrochloride. Following the procedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-proline hydrochloride (250 mg, 0.69 mmol) and 4-methoxybenzylamine (0.27 mL, 2.1 mmol) provided, after treatment with HCl in Et_2O, 90 mg of the title compound as a powder. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure. Rf = 0.38 (free base in EtOAc)
LSIMS [M-HCl] = 443 (mass calculated for $C_{24}H_{30}N_2O_6$ + HCl = 478.98).

Example 124



L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 3-Methoxybenzamide Hydrochloride. Following the procedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-proline hydrochloride (250 mg, 0.69 mmol) and 3-methoxybenzylamine (0.27 mL, 2.1 mmol) provided, after treatment with HCl in Et_2O, 90 mg of the title compound as a powder. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
R_f = 0.38 (free base in EtOAc)
LSIMS [M-HCl] = 443 (mass calculated for $C_{24}H_{30}N_2O_6$ + HCl = 478.98).

Example 125

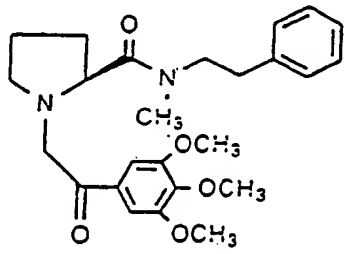


L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-Methoxybenzamide Hydrochloride. Following the procedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-proline hydrochloride (250 mg, 0.69 mmol) and 2-methoxybenzylamine (0.27 mL, 2.1 mmol) provided, after treatment with HCl in Et_2O, 120 mg of the title compound as a powder. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.

R_f = 0.38 (free base in EtOAc)

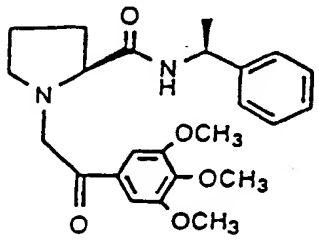
LSIMS [M-HCl] = 443 (mass calculated for $C_{24}H_{30}N_2O_6$ + HCl = 478.98).

Example 126



L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] N-Methylphenethylamide Hydrochloride. Following the procedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-proline hydrochloride (250 mg, 0.69 mmol) and N-methyl phenethylamine (0.30 mL, 2.1 mmol) provided, after treatment with HCl in Et_2O, 20 mg of the title compound as a powder. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure. LSIMS [M-HCl] = 441 (mass calculated for $C_{25}H_{32}N_2O_5$ + HCl = 477.00).

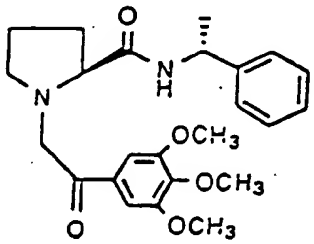
Example 127



L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] (S)-α-methylbenzylamide Hydrochloride. Following the procedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-proline hydrochloride (250 mg, 0.69 mmol) and (S)-(-)-α-methylbenzylamine (0.27 mL, 2.1 mmol) provided, after treatment with HCl in Et_2O, 160 mg of the title compound as a powder. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.

LSIMS [M-HCl] = 427 (mass calculated for $C_{24}H_{30}N_2O_5$ + HCl = 462.98).

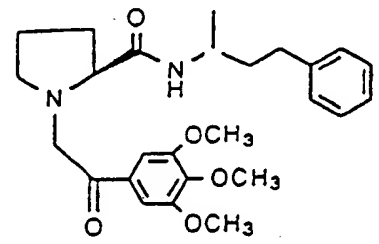
Example 128



L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] (R)-α-methylbenzylamide Hydrochloride. Following the procedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxo thyl]-L-proline hydrochloride (250 mg, 0.69 mmol) and (R)-(+)-α-methylbenzylamine (0.27 mL, 2.1 mmol) provided, after treatment with HCl in Et_2O, 190 mg of the title compound as a powder. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.

LSIMS [M-HCl] = 427 (mass calculated for $C_{24}H_{30}N_2O_5$ + HCl = 462.98).

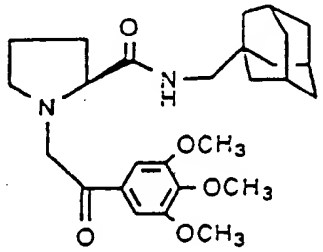
Example 129



L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 1-methyl-3-phenylpropylamide Hydrochloride. Following the procedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-proline hydrochloride (250 mg, 0.69 mmol) and 1-methyl-3-phenylpropylamine (0.34 mL, 2.1 mmol) provided, after treatment with HCl in Et_2O, 40 mg of the title compound as a foam. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.

LSIMS [M-HCl] = 455 (mass calculated for $C_{26}H_{34}N_2O_5$ + HCl = 491.03).

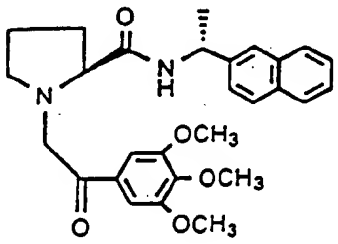
Example 130



L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] Adamant-1-ylmethylamide Hydrochloride. Following the procedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-proline hydrochloride (250 mg, 0.69 mmol) and 1-adamantylmethylamine (0.37 mL, 2.1 mmol) provided, after treatment with HCl in Et_2O, 100 mg of the title compound as a powder. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.

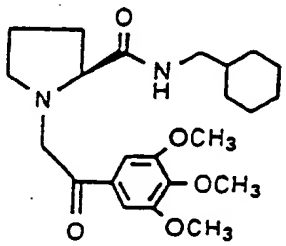
LSIMS [M-HCl] = 471 (mass calculated for $C_{27}H_{38}N_2O_5$ + HCl = 507.07).

Example 131



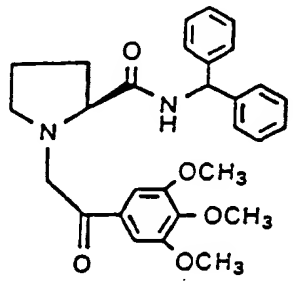
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 1-(R)-(1-naphthyl)ethylamide Hydrochloride. Following the procedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-proline hydrochloride *(250* mg, 0.69 mmol) and (R)-1-(1-naphthyl)ethylamine (0.34 mL, 2.1 mmol) provided, after treatment with HCl in Et_2O, 137 mg of the title compound as a powder. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
LSIMS [M-HCl] = 477 (mass calculated for $C_{28}H_{32}N_2O_5$ + HCl = 513.04).

Example 132



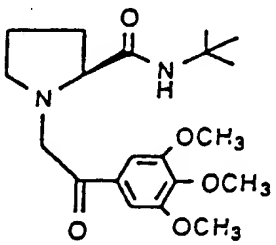
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] Cyclohexylmethylamide. Following the procedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-proline hydrochloride (250 mg, 0.69 mmol) and cyclohexylmethylamine (0.27 mL, 2.1 mmol), provided 138 mg of the title compound as a powder. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
LSIMS = 419 (mass calculated for $C_{24}H_{34}N_2O_5$ = 418.54).

Example 133



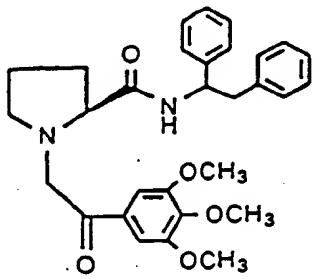
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] Diphenylmethylamide Hydrochloride. Following the procedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-proline hydrochloride (250 mg, 0.69 mmol) and aminodiphenylmethane (0.12 mL, 0.69 mmol) provided, after treatment with HCl in Et_2O, 132 mg of the title compound as a powder. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
LSIMS [M-HCl] = 489 (mass calculated for $C_{29}H_{32}N_2O_5$ + HCl = 525.05).

Example 134



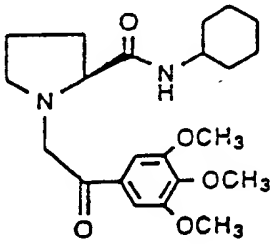
L-Prolin , 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] tert-Butylamide Hydrochlorid . Following the procedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-proline hydrochloride (250 mg, 0.69 mmol) and t-butylamine (0.22 mL, 2.1 mmol) provided, after treatment with HCl in Et_2O, 146 mg of the title compound as a powder. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
Rf = 0.42 (for free base: EtOAc)
LSIMS [M-HCl] = 379 (mass calculated for $C_{20}H_{30}N_2O_5$ + HCl = 414.93).

Example 135



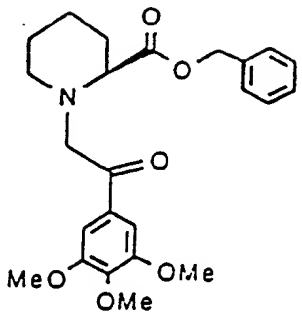
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 1,2 Diphenylethylamide Hydrochloride. Following the procedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-proline hydrochloride (250 mg, 0.69 mmol) and 1,2-diphenylethylamine (0.40 mL, 2.1 mmol) provided, after treatment with HCl in Et_2O, 95 mg of the title compound as a powder. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
Rf = 0.56 (free base in EtOAc)
LSIMS [M-HCl] = 503 (mass calculated for $C_{30}H_{34}N_2O_5$ + HCl = 539.07).

Example 136



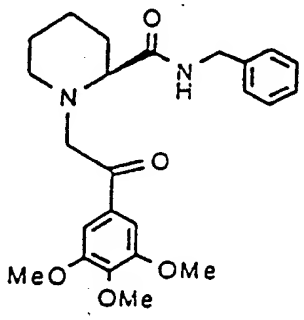
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] Cyclohexyl amide Hydrochloride. Following the procedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-proline hydrochloride (250 mg, 0.69 mmol) and cyclohexylamine (0.24 mL, 2.1 mmol) provided, after treatment with HCl in Et_2O, 147 mg of the title compound as a powder. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
Rf = 0.34 (free base in EtOAc)
LSIMS [M-HCl] = 405 (mass calculated for $C_{22}H_{32}N_2O_5$ + HCl = 440.97).

Exampl 137 (Not within the scope of the claims)



1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] L-Homoproline Benzyl Ester Hydrochloride. Using the procedure described in example 1e, L-homoproline benzyl ester tosylate salt (5.0 g, 12.77 mmol) and 3,4,5-trimethoxyphenyl α-bromomethyl ketone (7.4 g, 25.6 mmol) provided 5.4 g of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.

Example 138

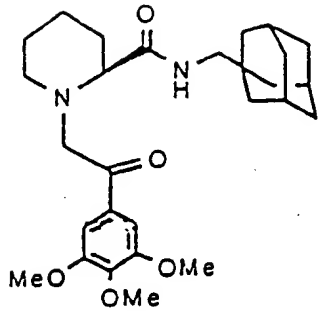


L-Homoproline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] Benzylamide Hydrochloride.

a) 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] L-Homoproline Benzyl Ester Hydrochloride. 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] L-Homoproline Benzyl Ester Hydrochloride was reductively cleaved using the procedure described in Example 118 to provide 4.46 g of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.

b) L-Homoproline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] Benzylamide Hydrochloride. Following the procedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-homoproline hydrochloride (200 mg, 0.53 mmol) and benzylamine (0.09 mL, 0.80 mmol) provided, after treatment with HCl in Et_2O, 112 mg of the title compound as a powder. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure.
LSIMS [M-HCl] = 427 (mass calculated for $C_{24}H_{30}N_2O_5$ + HCl = 462.98).

Example 139

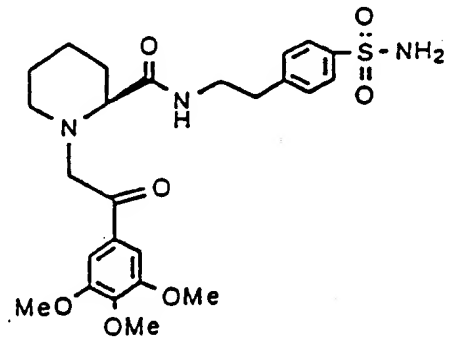


L-Homoproline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] Adamant-1-ylmethylamide Hydrochloride. Following the procedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-homoproline hydrochloride (200 mg, 0.53 mmol) and 1-adamantylmethylamine (0.19 mL, 1.07 mmol) provided, after treatment with HCl in Et_2O, 59 mg of the title compound as a powder. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
LSIMS [M-HCl] = 485 (mass calculated for $C_{28}H_{40}N_2O_5$ + HCl = 521.10).

Example 140

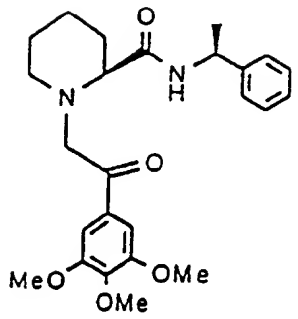
L-Homoproline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] tetrahydrofurfurylamide. Following the procedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-homoproline hydrochloride (200 mg, 0.53 mmol) and tetrahydrofurfurylamine (0.17 mL, 1.6 mmol), provided 100 mg of the title compound as a sticky solid. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
LSIMS = 421 (mass calculated for $C_{22}H_{32}N_2O_6$ = 420.51).

Example 141



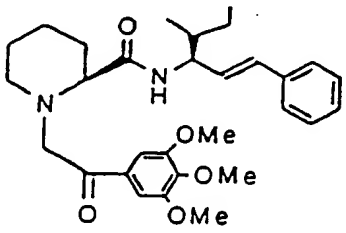
L-Homoproline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-(4-Sulfamoylphenyl)ethylamide. Following the procedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-homoproline hydrochloride (200 mg, 0.53 mmol) and 4-(2-aminoethyl)benzenesulfonamide (214 mg, 1.06 mmol) provided 25 mg of the title compound as a solid. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
LSIMS = 520 (mass calculated for $C_{25}H_{33}N_3O_7S$ = 519.62).

Example 142



L-Homoproline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] (S)-α-methylbenzylamide Hydrochloride. Following the procedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-homoproline hydrochloride (200 mg, 0.53 mmol) and (S)-(-)-α-methylbenzylamine (0.21 mL, 1.6 mmol) provided, after treatment with HCl in Et_2O, 107 mg of the title compound as a powder. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
LSIMS [M-HCl] = 441 (mass calculated for $C_{25}H_{32}N_2O_5$ + HCl = 477.00).

Example 143



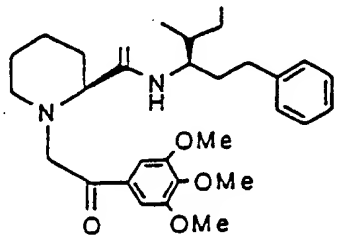
L-Homoproline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] (1-(S)-[2'-(S)-methylpropyl]-3-phenylprop-2-E-enyl)-amide.

a) *trans* 1-Phenyl-3-(S)-[[(1,1-dimethylethoxy)carbonyl]-amino]-4-(S)-methylhexa-1-ene. Into a 1-L round bottomed flask equipped with a magnetic stirrer was added diethyl benzylphosphonate (14.3 mL, 15.8 g, 69.37 mmol, 1.2 eq.) and THF (500 mL). The flask was purged with argon and cooled to -78 °C. A 1 M solution of $NaN(SiMe_3)_2$ in THF (74.1 mL, 74.1 mmol, 1.2 eq.) was added dropwise to the phosphonate, and the color changed from colorless to pale yellow. After stirring 30 min at -78 °C, a solution of Boc-L-isoleucinal (13.6 g, 63.1 mmol, prepared as described earlier: Saari, W.S.; Fisher, T. E. *Synthesis* 1990, 453-454.) in THF (50 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 30 min, then allowed to warm up to 0 °C over a 2 hour period. The solution was evaporated to dryness and the resulting colorless oil was dissolved in Et_2O (250 mL). The ether solution was washed with sat. aq. NH_4Cl (50 mL), sat. aq. NaCl (25 mL), dried ($MgSO_4$) and evaporated to a residue. The residue was purified by flash chromatography (5% EtOAc in hexane) to provide 8.7 g (48%) of the title compound as a colorless oil.
Rf = 0.63 (30% EtOAc in hexane).

b) *trans* 1-Phenyl-3-(S)-amino-4-(S)-methylhexa-1-ene. A solution of *trans* 1-phenyl-3-(S)-[[(1,1-dimethylethoxy) carbonyl]-amino]-4-(S)-methylhexa-1--ene (8.7 g, 30.27 mmol) was dissolved in CH_2Cl_2 (50 mL) and treated with trifluoroacetic acid (20 mL). After 20 min stirring at 22 °C, the reaction appeared complete (TLC). The reaction mixture was neutralized with excess sat. aq. $NaHCO_3$, washed with sat. aq. NaCl (20 mL), dried ($MgSO_4$) and evaporated to a residue. The resulting colorless oil was dissolved in Et_2O (100 mL) and extracted with 1 N HCl (3 x 50 mL). The aqueous layer was neutralized with 1 N NaOH and extracted with Et_2O (3 x 50 mL). The organic lay r was dried ($MgSO_4$) and conc ntrated in vacuo to provide 2.8 g (50%) of the title compound as a colorless oil that solidified on standing. Th ^1H NMR and Mass spectrum analysis of this compound was consistent with the structur . Rf = 0.04 (30% EtOAc in h xan).

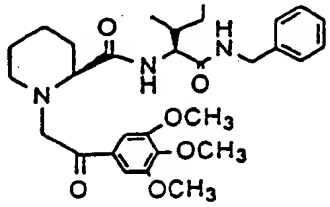
c) L-Homoproline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] (1-(S)-[2'-(S)-methylpropyl]-3-phenylprop-2-E-enyl)-amide. Following the procedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-homoproline hydrochloride (300 mg, 0.80 mmol) and trans 1-phenyl-3-(S)-amino-4-(S)-methylhexa-1-ene (228 mg, 1.2 mmol) provided 280 mg of the title compound as a solid. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure. LSIMS = 509 (mass calculated for $C_{30}H_{40}N_2O_5$ = 508.66).

Example 144



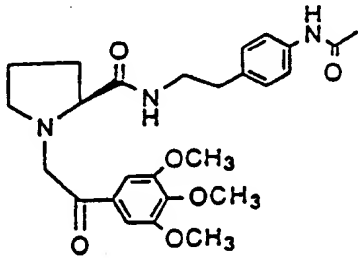
L-Homoproline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] (1-(S)-[2'-(S)-methylpropyl]-3-phenylpropyl)-amide. In a round bottomed flask equipped with a magnetic stirrer was added L-homoproline, 1-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl] (1-(S)-[2'-(S)-methylpropyl]-3-phenylprop-2-enyl)-amide (220 mg, 0.43 mmol), 10% palladium on carbon (22 mg), and methanol (50 mL) The flask was purged with hydrogen and the slurry stirred under an atmosphere of H_2 for 2 hours. The catalyst was removed by filtration through celite and the solvent removed in vacuo to provide 220 mg of the title compound. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure. LSIMS = 511 (mass calculated for $C_{30}H_{42}N_2O_5$ = 510.68).

Example 145



L-Isoleucine, N-[1-(2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl)-L-Homoprolyl] Benzylamide. Following the procedure described in Example 111b, the coupling of N-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-L-homoproline hydrochloride (200 mg, 0.53 mmol) and L-isoleucine benzylamide (118 mg, 0.53 mmol) provided 190 mg of the title compound as a solid. The 300 MHz, ^{1}H NMR analysis of this compound was consistent with the structure. LSIMS = 540 (mass calculated for $C_{30}H_{41}N_3O_6$ = 539.68).

Example 146



L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-(4-(N-Acetyl)aminophenyl)ethylamid . In an oven-dri d round bottomed flask was added L-proli , 1-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl] 2-(4-aminophenyl) thyla-

mide (100 mg, 0.23 mmol), and tetrahydrofuran (5 mL). The solution was stirred at 22 °C, and treated with pyridine (0.037 mL, 0.45 mmol, 2.0 eq) followed by acetyl chloride (0.024 mL, 0.34 mmol, 1.5 eq). The r action mixture was allowed to stir for one hour. The solvent was removed in vacuo and the residue partitioned between EtOAc (50 mL) and sat. $NaHCO_3$ (50 mL). The organic layer was washed with sat. aq. NaCl, dried ($MgSO_4$) and concentrated to an oil. The oil was purified by flash chromatography to provide 70 mg of the title compound as a foam. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
LSIMS = 484 (mass calculated for $C_{26}H_{33}N_3O_6$ = 483.57).

Example 147

L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl])-2-(4-(N-Benzoyl)aminophenyl)ethylamide. Following the procedure described in Example 146, treatment of L-proline, 1-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl] 2-(4-aminophenyl)ethylamide (100 mg, 0.23 mmol) with benzoyl chloride (0.039 mL, 0.34 mmol) provided 67 mg of the title compound as a foam. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
R_f = 0.35 (EtOAc)
LSIMS = 546 (mass calculated for $C_{31}H_{35}N_3O_6$ = 545.64).

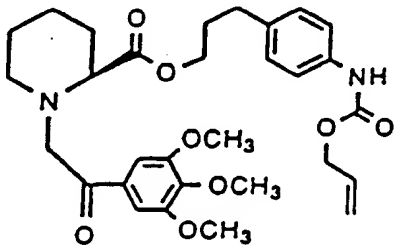
Example 148

L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-(4-(N-carboalloxy)aminophenyl)ethylamide. Following the procedure described in example 146, treatment of L-proline, 1-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl] 2-(4-aminophenyl)ethylamide (100 mg, 0.23 mmol) with allyl chloroformate (0.036 mL, 0.34 mmol) provided 90 mg of the title compound as a foam. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
Rf = 0.42 (EtOAc)
LSIMS = 526 (mass calculated for $C_{28}H_{35}N_3O_7$ = 525.61).

Example 149

L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-(4-(N-Carbobenzyloxy)aminophenyl)ethylamide. Following the procedure described in Example 146, treatment of L-proline, 1-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl] 2-(4-aminophenyl)ethylamide (80 mg, 0.18 mmol) with benzyl chloroformate (0.039 mL, 0.27 mmol) provided 72 mg of the title compound as a foam. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
Rf = 0.42 (EtOAc)
LSIMS = 577 (mass calculated for $C_{32}H_{37}N_3O_7$ = 575.67).

Example 150 (Not within the scope of the claims)



L-Homoproline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 3-(4-(N-Carboallyloxy)aminophenyl)propyl Ester Hydrochloride.

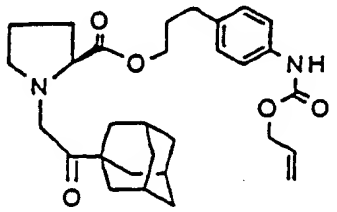
a) N-Carbo-*tert*-butoxy-L-homoproline 3-(4-(N-Carboallyloxy)aminophenyl)propyl Ester. To an oven-dried round bottomed flask was added N-carbotertbutoxy-L-pipecolinc acid (500 mg, 2.2 mmol), 1.0 eq benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (966 mg, 2.2 mmol), 3-(4-(N-carboallyloxy)aminophenyl)-propanol (514 mg, 2.2 mmol) and anhydrous dichloromethane (20 mL). The solution was cooled to 0 °C and treated with triethylamin (0.92 mL, 6.6 mmol, 3.0 q). After stirring for 3 hours at 0 °C, the reaction mixture was diluted with dichloromethane (100 mL), washed with 5% citric acid (100 mL), sat. $NaHCO_3$ (100 mL), sat. aq. NaCl (100 mL), and dried ($MgSO_4$). The solution was concentrated in vacuo, and purified by flash chromatography to provide

740 mg of th titl compound. This material was used directly for the next reaction.

b) L-Homoproline 3-(4-(N-Carboallyloxy)aminophenyl)propyl Ester Trifluoroacetate Salt. This material from example 150a was dissolved in ether (20 mL) and treated with trifluoroacetic acid (2 mL) and allowed to stir at 22 °C for 17 hours. The solvent was removed in vacuo and the residu triturated three times with ether and dried to provide 220 mg of L-homoproline 3-(4-(N-carboallyloxy)aminophenyl)propyl ester as the trifluoroacetic acid salt. This compound was used directly for the next reaction.

c) L-Homoproline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 3-(4-(N-Carboallyloxy)aminophenyl)propyl Ester Hydrochloride. In an oven-dried flask, was added L-homoproline 3-(4-(N-carboallyloxy)aminophenyl)-propyl ester as the trifluoroacetic acid salt (200 mg), 3,4,5-trimethoxyphenyl-2-bromoacetophenone, and THF (20 mL). The slurry was treated with triethylamine (0.3 mL, 2.2 mmol, 5 eq) and heated to reflux for 4 hours. The solvent was removed in vacuo and the residue was taken up in EtOAc (100 mL) and washed with sat. $NaHCO_3$ (100 mL), sat. aq. NaCl (100 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography to provide the free amine (Rf = 0.44; 30% EtOAc in hexane) which was treated with HCl in ether and dried in vacuo to provide 60 mg of the title compound as a solid. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
LSIMS [M-HCl] = 555 (mass calculated for $C_{30}H_{38}N_2O_8$ + HCl = 591.10).

Example 151 (Not within the scope of the claims)



L-Proline, 1-[2-Adamantan-1-yl-2-Oxoethyl] 3-(4-(N-Carboallyloxy) aminophenyl)propyl Ester Hydrochloride.

a) N-Carbo-*tert*-butoxy-L-proline 3-(4-(N-Carboallyloxy)aminophenyl)-propyl ester. Following the procedure described in Example 150a, the coupling of N-Carbo-*tert*-butoxy-L-proline (457 mg, 2.1 mmol) and 3-(4-(N-carboallyloxy)aminophenyl)propanol (500 mg, 2.1 mmol) provided 580 mg of the Boc-protected intermediate.

b) This intermediate from Example 151a was deprotected with 1 N HCl in ether (20 mL) and the mixture was allowed to stir for 17 hours at 22 °C. The solution was concentrated in vacuo to provide 490 mg of the corresponding hydrochloride salt.

c) L-Proline, 1-[2-Adamantan-1-yl-2-Oxoethyl] 3-(4-(N-Carboallyloxy) aminophenyl)propyl Ester Hydrochloride. A portion of the hydrochloride salt (195 mg, 0.53 mmol) was treated with 1-adamantyl α-bromomethyl ketone (272 mg, 1.06 mmol), using the procedure described in Example 150c. This provided the free amine which was treated with HCl in ether and dried in vacuo to provide 90 mg of the title compound as a solid. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
Rf = 0.38 (for free base: 50% EtOAc in hexane).
LSIMS [M-HCl] = 509 (mass calculated for $C_{30}H_{40}N_2O_5$ + HCl = 545.12).

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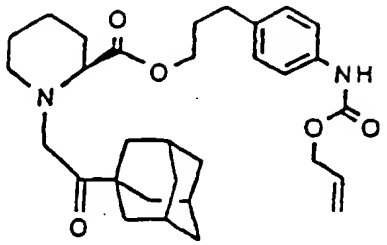
Example 152 (Not within th scope of the claims)



L-Homoproline, 1-[2-Adamant-1-yl-2-Oxoethyl] 3-(4-(N-Carboallyloxy)aminophenyl)propyl Ester Hydrochloride. Following the procedure described in Example 150c, 3-(4-(N-carboallyloxy) aminophenyl)propyl pipecolinate, trifluoroacetic acid salt (220 mg, 0,48 mmol) and 1-adamantyl α-bromomethyl ketone (250 mg, 0.97 mmol) provided the amine which was treated with HCl in ether to provide 40 mg of the title compound as a powder. The 300 MHz, ^1H NMR analysis of this compound was consistent with the structure.
LSIMS [M-Cl] = 523 (mass calculated for $C_{31}H_{42}N_2O_5$ + HCl = 559.15).

The immunosuppressive properties of the present compounds were evaluated in the following assays:

1) Inhibition of PPIase Activity

This assay follows in principle the procedure described in Kofron et al., 1991, Biochemistry 30:6127.

The three main reagents used are PPIase, a substrate for PPIase, and a selected inhibitor compound of the present invention. The basic principle behind this assay is the conversion of the cis isomer of the substrate to the trans form, which conversion is catalyzed by PPIase. Essentially, inhibition of this PPIase activity is measured for the selected compounds. A peptide chymotrypsin substrate containing a proline in the P2 position is only cleaved by chymotrypsin when the Phe-Pro bond is in the trans isomeric configuration. In the presence of excess chymotrypsin, all of the trans peptide isomers are cleaved within approximately five seconds, leaving only cis forms.

The cis peptide will spontaneously convert to the trans isomer at a slow rate. The cis to trans conversion is catalyzed by isomerases at a much faster rate than this spontaneous conversion. Proteins with PPIase activity are examples of such isomerases. After isomerization, the peptide is cleaved by chymotrypsin releasing p-nitroaniline which can be monitored at 390 nm. The rate of release is then calculated using a first order rate plus offset equation utilizing the ENZFITTER program (Leatherbarrow, BIOSOFT, Cambridge, United Kingdom).

Example 153

PPIase Inhibition Assay

In a plastic cuvette are added 950 ul of ice cold assay buffer (25 mM HEPES, pH 7.8, 100 mM NaCl), 10 uL of FKBP (2.5 uM in 10 mM Tris-Cl pH 7.5, 100 mM NaCl, 1 mM dithiothreitol), 25 ul of chymotrypsin (50 mg/ml in 1 mM HCl) and 10 ul of the test compound at various concentrations in dimethyl sulphoxide. The reaction is initiated by addition of 5 ul of substrate (Succinyl-Ala-Phe-Pro-Phe-para-nitroanilide, 5 mg/ml in 235 mM LiCl in trifluoroethanol).

The absorbance at 390 nm versus time is monitored for 90 sec using a Beckman DU70 spectrophotometer. The absorbance versus time data files are transferred to an IBM XT computer and the rate constants determined using the commercial Enzfitter program. For each set of data, the uncatalyzed rate of conversion is measured and the uninhibited enzymatic rate determined. The data are expressed as % Inhibition and are calculated as follows:

$$\% \text{ Inhibition} = \left[1 - \frac{(k_{obs} - k_{uncat})}{(k_{uninh} - k_{uncat})} \right] X \quad 100$$

where k_{obs} is the rate in the presence of a selected test compound, k_{uncat} is the rate in the absence of enzyme, and k_{uninh} is the rate in the presence of enzyme and absence of inhibitor. Data are plotted as percent inhibition versus

concentration of inhibitor. The values of the concentration of inhibitor required for 50% inhibition of enzyme activity (IC_{50}) were determined by nonlinear least squares regression analysis.

TABLE I

Example No.	(IC_{50}) μM
Example 1	2.2
Example 2	<50
Example 3	2.7
Example 4	3.4
Example 5	<50
Example 6	<50
Example 7	50
Example 8	5.8
Example 9	<50
Example 10	<50
Example 11	<50
Example 12	>50
Example 13	<50
Example 14	<50
Example 15	<50
Example 16	<50
Example 17	<50
Example 18	>50
Example 19	<50
Example 20	0.06
Example 21	0.99
Example 22	<50
Example 23	12
Example 24	<50
Example 25	<50
Example 26	<50
Example 27	<5
Example 28	<5
Example 29	5
Example 30	<5
Example 31	>5
Example 32	2.2
Example 33	>50
Example 34	n.d.
Example 35	15
Example 36	<5
Example 37	<5
Example 38	>5
Example 39	<5
Example 40	<5

Example No.	(IC_{50}) μM
Example 41	<5
Example 42	<5
Example 43	ND
Example 44	50
Example 45	>50
Example 46	<50
Example 47	>50
Example 48	>50
Example 49	5.1
Example 50	1.2
Example 51	0.22
Example 52	2.3
Example 53	0.71
Example 54	0.4
Example 55	<5
Example 56	1.3
Example 57	0.3
Example 58	<5
Example 59	0.1
Example 60	0.1
Example 61	0.71
Example 62	0.4
Example 63	0.2
Example 64	0.64
Example 65	>5
Example 66	<5
Example 67	<5
Example 68	<5
Example 69	<5
Example 70	>5
Example 71	<5
Example 72	>5
Example 73	>5
Example 74	>5
Example 75	>5
Example 76	<5
Example 77	>5
Example 78	3.2
Example 79	<5
Example 80	0.88

where ND means "not determined"

TABLE 1 (Contd.)

Example No.	(IC_{50}) μM
Example 81	>5
Example 82	<5
Example 83	0.12
Example 84	<5
Example 85	<5
Example 86	0.6
Example 87	1.2
Example 88	<5
Example 89	<5
Example 90	<5
Example 91	5
Example 92	>5
Example 93	<5
Example 94	5
Example 95	<5
Example 96	<5
Example 97	<5
Example 98	<5
Example 99	<5
Example 100	<5
Example 101	<5
Example 102	<5
Example 103	<5
Example 104	<5
Example 105	<5
Example 106	<5
Example 107	>5
Example 108	<5
Example 109	<5
Example 110	ND
Example 111	>5
Example 112	>5
Example 113	>5
Example 114	>5
Example 115	>5
Example 116	>5

Example No.	(IC_{50}) μM
Example 117	>5
Example 118	>5
Example 119	>5
Example 120	>5
Example 121	>5
Example 122	>5
Example 123	>5
Example 124	>5
Example 125	>5
Example 126	>5
Example 127	>5
Example 128	>5
Example 129	>5
Example 130	>5
Example 131	>5
Example 132	>5
Example 133	>5
Example 134	>5
Example 135	>5
Example 136	>5
Example 137	ND
Example 138	>5
Example 139	>5
Example 140	>5
Example 141	>5
Example 142	>5
Example 143	>5
Example 144	>5
Example 145	ND
Example 146	>5
Example 147	>5
Example 148	>5
Example 149	>5
Example 150	>5
Example 151	>5
Example 152	>5

where ND means "not determined"

Results: The results of the compound testing are presented in TABLE 1, above. As stated previously, it was not initially apparent whether or not inhibition of PPIase activity was necessary and sufficient for immunosuppression. Presently, the prevailing thought is that binding to the PPIase enzyme may be necessary but is not sufficient. Therefore, the data on PPIase inhibition may be viewed as an assay to detect whether or not a given compound is capable of interacting productively with FKBP.

2) Human T Lymphocyte Inhibition

Inhibition of mitogen-induced T-cell proliferation can be used to profile immunosuppressive activity of test compounds. In the description of the assay which follows, mitogen-induced T-cell proliferation was used to test the inhibitory potencies of select compounds of the present invention.

In an assay similar to that described by Bradley in Mishell et al. (Eds.), 1980, Selected Methods in Cellular Immunology, pp 156-161, W.H. Freeman & Co., San Fransisco, CA., T-cells were stimulated by incubation with phytohemagglutinin (PHA) with binds to cell surface molecules, including the T-cell receptor. This stimulation results in proliferation which can be measured by incorporation of [^{3}H]-thymidine into cellular DNA.

The immunosuppressive properties of the compounds of the present invention can be determined by adding various concentrations of the compounds to these cultures and measuring the effect on T-cell proliferation.

Example 154

Suppression of Human T-Cell Proliferation Assay

Fresh LeukoPaks were obtained from the New York Blood Center, New York, NY. The cells, including erythrocytes and leukocytes, were diluted with Hank's Balanced Salt Solution (HBSS) (GIBCO, Grand Island, NY) and layered over Lymphoprep (Nycomed Pharma AS, Oslo, Norway) in sterile 50 ml conical centrifuge tubes. Lymphocytes were isolated at the Hank's/Nycomed interface after centrifugation at 2000 X g, 4 oC for 15 min. The lymphocytes were washed with Minimal Essential Medium (GIBCO) containing 2% fetal bovine serum (FBS) (Sigma Chemical Co., St. Louis, MO), 1% HEPES buffer (GIBCO) and 1% Penicillin-Stretomycin solution (GIBCO).

T-cells were further purified essentially by sheep erythrocyte (SRBC) rosetting as described by Morimoto et al., 1983, J. Immunol. 130:157. The isolated lymphocytes were adjusted to 2 X 10^7 cells/ml and 5 ml aliquots of the cell suspension were incubated for 10 minutes at room temperature with 5 ml of a 5% SRBC (Cappel, Organon Technika Corp., West Chester, PA) suspension. The cells were gently pelleted by centrifugation at 300 rpm for 10 minutes, followed by a 1 hour incubation at room temperature to allow rosette formation. The cells were gently resuspended, layered over Lymphoprep and centrifuged for 30 minutes at 500 X g. The pellet, containing rosetted T-cells and SRBC was treated with ice cold buffered ammonium chloride (GIBCO) to lyse the erythrocytes. T-cells were washed twice with HBSS.

Purified T-cells were resuspended at 2 X 10^6 cells /ml in complete culture medium composed of RPMI-1640 (Whittaker Bioproducts, Walkerville, MD) with 10% FBS (Sigma), 2 mM L-glutamine (GIBCO), 1% Penicillin-Streptomycin (GIBCO) and 15 mM HEPES (GIBCO). In 96-well plates (Becton Dickinson, Lincoln Park, NJ), 0.1 ml aliquots of T-cell suspension were mixed with 0.05 ml of 40 µg/ml PHA-M (Sigma). The compounds of this invention were dissolved in dimethylsulfoxide at 10 mM and various dilutions in complete medium were added in duplicate wells (0.05 ml/well). The plates were incubated at 37 °C in a humidified atmosphere of 5% carbon dioxide and 95% air for 72 hours.

Proliferation was assessed by measurement of [^{3}H]-thymidine incorporation. During the last 6 hours of incubation, the cells were pulse labelled with 1µCi/well of [^{3}H]-thymidine (New England Nuclear, Boston, MA). The cells were harvested onto glass fiber paper using a plate harvester and the radioactivity incorporated into cellular DNA corresponding to individual wells was measured by standard liquid scintillation counting methods. The mean counts per minute (CPM) of replicate wells was calculated and linear regression analysis of mean CPM versus compound concentration was used to determine the concentration of compound which would inhibit [^{3}H]-thymidine incorporation of T-cells by 50% (IC_{50}).

The results of this assay, presented in Table 2, are representative of the intrinsic immunosuppresive activity of the compounds of the present invention. Thus, concentrations less than 10 µM of some of the preferred compounds suppress the T-cell proliferative response by 50%.

TABLE 2

Example No.	(IC_{50}) μM
Example 1	ND
Example 2	ND
Example 3	<50
Example 4	50
Example 5	50
Example 6	<50
Example 7	34
Example 8	35
Example 9	>50
Example 10	>50
Example 11	17
Example 12	>50
Example 13	>50
Example 14	6
Example 15	18
Example 16	<11
Example 17	34
Example 18	42
Example 19	62
Example 20	12
Example 21	63
Example 22	58
Example 23	20
Example 24	ND
Example 25	ND
Example 26	ND
Example 27	32
Example 28	41
Example 29	42
Example 30	40
Example 31	43
Example 32	20
Example 33	>100
Example 34	ND
Example 35	6
Example 36	17
Example 37	6
Example 38	7
Example 39	16
Example 40	12

Example No.	(IC_{50}) μM
Example 41	20
Example 42	13
Example 43	ND
Example 44	ND
Example 45	ND
Example 46	>50
Example 47	16
Example 48	ND
Example 49	13
Example 50	8
Example 51	8
Example 52	7
Example 53	10
Example 54	16
Example 55	17
Example 56	4
Example 57	6
Example 58	7
Example 59	8
Example 60	3
Example 61	19
Example 62	16
Example 63	8
Example 64	7
Example 65	>50
Example 66	ND
Example 67	>50
Example 68	<50
Example 69	37
Example 70	>50
Example 71	28
Example 72	100
Example 73	ND
Example 74	ND
Example 75	ND
Example 76	20
Example 77	7
Example 78	>100
Example 79	22
Example 80	22

where ND means "not determined"

TABLE 2 (Contd.)

Example No.	(IC_{50}) μM
Example 81	8
Example 82	16
Example 83	8
Example 84	6
Example 85	4
Example 86	6
Example 87	6
Example 88	8
Example 89	12
Example 90	7
Example 91	>15
Example 92	>15
Example 93	>15
Example 94	>15
Example 95	>15
Example 96	>15
Example 97	>15
Example 98	≥15
Example 99	1
Example 100	>15
Example 101	5
Example 102	6
Example 103	7
Example 104	7
Example 105	8
Example 106	7
Example 107	7
Example 108	6
Example 109	>15
Example 110	ND
Example 111	7
Example 112	7
Example 113	8
Example 114	10
Example 115	>15
Example 116	>15
Example 117	10
Example 118	>15
Example 119	4
Example 120	10
Example 121	4
Example 122	22
Example 123	24
Example 124	22
Example 125	19
Example 126	14
Example 127	7
Example 128	16
Example 129	18
Example 130	4
Example 131	10
Example 132	7
Example 133	12
Example 134	3
Example 135	19
Example 136	4
Example 137	ND
Example 138	>15
Example 139	8
Example 140	>15
Example 141	>15
Example 142	>15
Example 143	4
Example 144	8
Example 145	>15
Example 146	13
Example 147	9
Example 148	6
Example 149	5
Example 150	10
Example 151	>15
Example 152	9

where ND means "not determined"

3) NF-AT Assay

Stimulation of T-cells leads to the appearance of several transcription factors, including one designated "NF-AT". These factors are involved in regulation of gene expression required for immunologic activation. Some of these transcription factors appear to have functions in a wide variety of cell types. By contrast, NF-AT is found primarily in T-cells and its role is restrict d to early gen activation. In addition, NF-AT activity is inhibited by the immunosuppressant drugs, Cyclosporin A and FK506 (Schreiber and Crabtree, 1992, Immunology Today 13:136).

Inhibition of NF-AT activity is measured using FGL-5 cells. FGL-5 is a cloned line of stably transfected Jurkat T-

cells that contain a construct in which three tandem copies of the NF-AT DNA binding site direct transcription of the lacZ gene, encoding β-galactosidase (Fiering et al., 1990, Genes & Development 4:1823). When these cells are stimulated with phorbol esters which activate protein kinase C and calcium ionophore to raise the intracellular calcium concentration, transcriptionally active NF-AT is produced. In T-cells, this normally leads to the expression of IL-2, T-cell growth factor. However, in FGL-S cells NF-AT activation leads of the production of β-galactosidase which can be detected using an appropriate substrate.

FGL-5 cells were cultured with phorbol ester, calcium ionophore and the compounds of the present invention to measure inhibition of β-galactosidase activity, as shown below.

Example 155

NF-AT Inhibition Assay Directed β-Galactosidase Expression

This assay was performed essentially as described (Bierer et al., 1990, Proc. Natl. Acad. Sci. 87:9231). FGL-5 cells were maintained in medium consisting of RPMI-1640 with 10% FBS, 2 mM L-glutamine, 1% Penicillin-Streptomycin and 15 mM HEPES buffer. The assays were done with exponentially growing cells whose density was not greater than 0.5 million cells/ml. The cells were resuspended to 3 million cells/ml in medium and 0.1 ml was added to wells of a 96-well plate.

The compounds of the present invention were dissolved in either ethanol or dimethylsulfoxide at 10 mM and 0.05 ml/well of various dilutions in medium were added to cells in duplicate wells. Treatment controls consisted of duplicate wells to which 0.05 ml/well of either medium, ethanol or dimethylsulfoxide was added. The ethanol and dimethyl sulfoxide were at the same concentration as was used for the compounds. Cells were incubated with compounds at room temperature for 10 - 15 minutes. Phorbol dibutyrate (Sigma) and Ionomycin (Calbiochem) were dissolved at 50 µg/ml and 2 mM, respectively and stored at -70 °C.

FGL-5 cells were stimulated by diluting these reagents with medium to 200 ng/ml and 8 µM, respectively and adding of 0.05 ml/well. For unstimulated cell controls, 0.05 ml/well of medium was added to duplicate wells. The plates were incubated overnight (16-18 hours) at 37 °C in a humidified atmosphere of 5% CO_2 and air.

β-galactosidase activity was measured as the fluorescence generated by the cleavage of 4-methyl umbelliferyl-β-D-galactoside (Sigma) at the β-galactoside bond. After overnight incubation, the cells were centrifuged at 500 x g for 3 minutes in the 96-well plates and washed 3 times with PBS. The cells were then resuspended in 0.18 ml/well of reaction medium containing 100 mM sodium phosphate buffer, pH 7.0, 10 mM potassium chloride, 1 mM magnesium sulfate, 0.1% Triton X-100 (Pierce, Rockford, IL), and 0.5 mM 4-methylumbelliferyl-β-D- galactoside.

The fluorescence at 460 nm using 355 nm excitation was measured at intervals over 1-2 hours (during which fluorescence increased linearly with time) with a LS50 Luminescence Spectrometer (Perkin Elmer).

The percent inhibition by each concentration of the compounds was calculated as:

$$\% \text{ Inhibition} = \frac{1-(\text{fluorescence with compound - unstimulated control})}{(\text{fluorescence with solvent alone - unstimulated control})} \times 100$$

The values of the concentration of compounds required for 50% inhibition (IC_{50}) were determined by linear regression analysis of the percent inhibition at various compound concentrations.

The results of this assay presented in TABLE 3 are representative of the intrinsic immunosuppresive activity of the compounds of the present invention. Compounds that inhibited NF-AT directed β-galactosidase expression by stimulated FGL-5 cells with IC_{50} of 10 µM or less also inhibited mitogen induced T-cell proliferation.

TABLE 3

Example No.	(IC_{50}) μM
Example 1	ND
Example 2	ND
Example 3	ND
Example 4	ND
Example 5	ND
Example 6	ND
Example 7	ND
Example 8	ND
Example 9	ND
Example 10	ND
Example 11	ND
Example 12	ND
Example 13	ND
Example 14	ND
Example 15	ND
Example 16	ND
Example 17	ND
Example 18	ND
Example 19	ND
Example 20	ND
Example 21	ND
Example 22	ND
Example 23	ND
Example 24	ND
Example 25	ND
Example 26	ND
Example 27	ND
Example 28	ND
Example 29	ND
Example 30	ND
Example 31	ND
Example 32	13
Example 33	>100
Example 34	ND
Example 35	41
Example 36	19
Example 37	13
Example 38	22
Example 39	14
Example 40	24

Example No.	(IC_{50}) μM
Example 41	>33
Example 42	15
Example 43	ND
Example 44	ND
Example 45	ND
Example 46	ND
Example 47	ND
Example 48	ND
Example 49	44
Example 50	73
Example 51	>100
Example 52	20
Example 53	>100
Example 54	18
Example 55	>100
Example 56	13
Example 57	20
Example 58	16
Example 59	17
Example 60	57
Example 61	>100
Example 62	60
Example 63	16
Example 64	16
Example 65	ND
Example 66	ND
Example 67	ND
Example 68	ND
Example 69	ND
Example 70	ND
Example 71	ND
Example 72	ND
Example 73	ND
Example 74	ND
Example 75	ND
Example 76	ND
Example 77	12
Example 78	>100
Example 79	13
Example 80	13

where ND means "not determined"

TABLE 3 (Contd.)

Example No.	(IC_{50}) μM
Example 81	6
Example 82	13
Example 83	5
Example 84	>100
Example 85	26
Example 86	6
Example 87	6
Example 88	8
Example 89	12
Example 90	7
Example 91	>15
Example 92	>15
Example 93	>15
Example 94	>15
Example 95	>15
Example 96	>15
Example 97	>15
Example 98	>15
Example 99	1
Example 100	>15
Example 101	5
Example 102	6
Example 103	7
Example 104	7
Example 105	8
Example 106	7
Example 107	7
Example 108	6
Example 109	>15
Example 110	ND
Example 111	7
Example 112	7
Example 113	8
Example 114	10
Example 115	>15
Example 116	>15

Example No.	(IC_{50}) μM
Example 117	10
Example 118	>15
Example 119	4
Example 120	>15
Example 121	>15
Example 122	>33
Example 123	>33
Example 124	>33
Example 125	>33
Example 126	>33
Example 127	>33
Example 128	>33
Example 129	>33
Example 130	>33
Example 131	>33
Example 132	>33
Example 133	>33
Example 134	>33
Example 135	>33
Example 136	>33
Example 137	ND
Example 138	>15
Example 139	>15
Example 140	>15
Example 141	>15
Example 142	>15
Example 143	>15
Example 144	>15
Example 145	>15
Example 146	>15
Example 147	>15
Example 148	>15
Example 149	>15
Example 150	3
Example 151	>15
Example 152	>15

where ND means "not determined"

4) Graft versus Host Assay

Inhibition of the graft versus host response (herinafter "GVHR") by the compounds of the present invention is another means to demonstrate their immunosuppressiv activity. Transfer of parental strain T-cells (the graft) into F1 hybrid animals (the host) different with respect to gene products of the major histocompatibility complex (MHC) causes a GVHR. This reaction results from recognition of host allogeneic MHC gene products by specific clon s of graft T-cells.

When given systemically in sufficient numbers, the graft T-cells cause a progressive, generally fatal, wasting syndrome. A local, nonfatal GVHR, marked by enlargement of the draining popliteal lymph nodes, ensues when graft T-cells are administered via the footpad as described by Ford et al., 1970, Transplantation 10:258. The GVHR is regarded as a correlate of allograft rejections where specific T-cells of either host or allograft origin are activated after recognition of allogeneic MHC gene product, leading to an immune inflammatory response which ultimately results in the destruction (rejection) of the allograft.

Example 156

Mouse Lymph Node Assay for Modulation of Graft versus Host Response

Single cell suspensions in phosphate buffered saline (PBS) were prepared from the spleens of BDF1 and C57B1\6 mice (Jackson Labs, Bar Harbor, ME). The cells were pelleted by centifugation at 500 X g for 5 minutes and the pellet resuspended in 0.9 ml distilled water to lyse erythrocytes. After 5 seconds, 0.1 ml 10X concentrated PBS was added, resulting in an isotonic solution. The cells were washed with PBS and resuspended at 2 X 10^8 cells/ml. 1 X 10^7 cells in 0.05 ml PBS were injected subcutaneously into the hind footpads (BDF1 cells in one footpad, C57B1/6 cells in the other). The test compounds were dissolved in ethanol, mixed with olive oil (1:7, ethanol:olive oil). Some mice received intraperitoneal injections (0.2 ml/injection) of either ethanol:olive oil alone (vehicle control group) or compound at 100 mg/kg per day, beginning on the same day as the spleen cell injections.

After 7 days, the draining popliteal lymph nodes from the hind limbs were dissected out and weighed. The magnitude of the GVHR was expressed as the ratio of the mean weight of lymph nodes from the limb injected with semiallogeneic C57B1/6 cells divided by the mean weight of lymph nodes from the limb injected with syngeneic BDF1 cells.

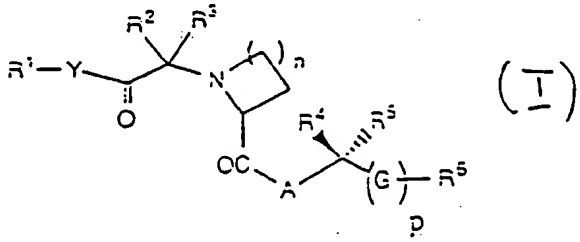
The results presented in TABLE 4 show that a representative compound of this invention which is a potent inhibitor of both FKBP activity and mitogen-induced T-cell proliferation also inhibited the localized GVHR. Thus, for the untreated or vehicle control groups, the mean lymph node weights from BDF1-sensitized limbs were 2.2 - 3.1 times that of C57B1/6-sensitized limbs. By contrast, in mice treated with the test compound, virtually no GVHR was detected (ratio=1.2). For comparison, in this example a group of mice was treated with 100 mg/kg/day of cyclosporin A (Sandoz Ltd., Basel, Switzerland). Cyclosporin A also inhibited the GVHR (ratio=1.6).

TABLE 4

Treatment	Lymph Node Weight Ratio
None	3.1
Vehicle alone	2.2
Compound of Example 16	1.2
Cyclosporin A	1.6

Claims

1. A compound of the following structure



(I)

wherein

R^1 is

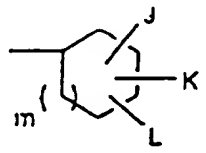
a) hydrogen,
b) linear or branched alkyl (C1-C8) which may be substituted independently or simultaneously up to two times by

i) hydroxy,
ii) phenyl which may be substituted by straight or branched alkyl (C1-C8), or straight or branched alkoxy (C1-C6),
iii) cycloalkyl (C3-C10) which may be substituted by straight or branched alkyl (C1-C8), or straight or branched alkoxy (C1-C6),
iv) bicycloalkyl (C6-C12) which may be substituted by straight or branched alkyl (C1-C10), or straight or branched alkoxy (C1-C6),
v) tricycloalkyl (C7-C14) which may be substituted by straight or branched alkyl (C1-C8), or straight or branched alkoxy (C1-C6),
vi) tetracycloalkyl (C10-C14), which may be substituted by straight or branched alkyl (C1-C8), or straight or branched alkoxy (C1-C6), or
vii) morpholinyl,

c) alkene (C3-C10), diene (C4-C10), or triene (C8-C18), which may be substituted independently or simultaneously up to three times by

i) phenyl,
ii) straight or branched alkyl (C1-C6), or
iii) straight or branched alkoxy (C1-C6),

d) cycloalkyl (C5-C10), or the cycloalkyl fragment



where

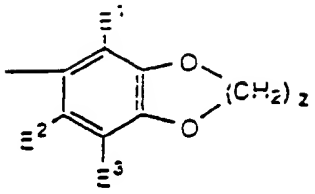
m is an integer of 0, 1, or 2,
J, K, and L are independently or simultaneously

i) hydrogen,
ii) straight or branched alkyl (C1-C5), which may be substituted by phenyl, or straight or branched alkoxy (C1-C6),
iii) straight or branched alkoxy (C1-C5),
iii) phenyl, or
iv) phenyl substituted by straight or branched alkyl (C1-C6), or chlorine, or straight or branched alkoxy (C1-C6),

e) bicycloalkyl (C7-10), tricycloalkyl (C7-14), tetracycloalkyl (C10-C16), or pentacycloalkyl (C11-C20), which may be independently or simultaneously substituted up to 3 times with straight or branched alkyl (C1-C6), or straight or branched alkoxy (C1-C6), or phenyl,
f) the aryl derivatives tetrahydronaphthyl, benzothienyl, benzofuryl, benzopyranyl, furyl, pyridyl, pyranyl, 1,3-oxazolyl, or naphthyl, said aryl derivatives may be independently or simultaneously substituted up to two times by

i) straight or branched alkyl (C1-C6),
ii) straight or branched alkoxy (C1-C6),
iii) halogen, wh r halogen is fluoro, chloro, bromo, or iod ,

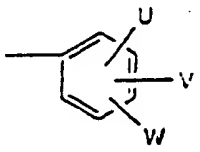
g) the piperonyl fragment



where

z is an integer of 1, or 2,
and E^1, E^2, and E^3 can independently or simultaneously be hydrogen, straight or branched alkyl (C1-C6), straight or branched alkoxy (C1-C6), or chlorine, or

h) the aryl derivative

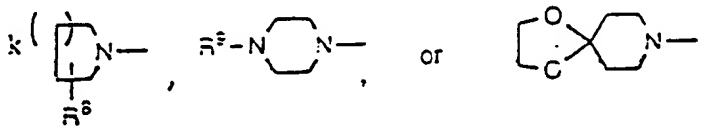


where

U, V, and W can be independently or simultaneously

i) hydrogen,
ii) straight or branched alkyl (C1-C6), straight or branched alkoxy (C1-C6), phenyl, or phenoxy, these groups may be substituted by phenyl, straight or branched alkoxy (C1-C6), or phenoxy,
iii) hydroxy,
iv) halogen,
v) nitro, or
vi) benzoyl;

Y is a covalent bond, oxygen, NR^7, where R^7 is hydrogen,
in addition,
R^1-Y- may also be



where

k is an integer of 1 or 2,
R^8 is

a) hydrog n,
b) carboalkoxy with a straight or branched alkoxy (C1-C6),
c) straight or branched akyl (C1-C6) which may be substituted by phenyl, or straight or branched

alkoxy (C1-C6),
d) phenyl, or phenyl substituted by halogen,

R^9 is phenyl which may be substituted by straight or branched alkyl (C1-C6);
R^2 and R^3 are defined as follows: one of R^2 and R^3 are hydrogen, and the other is hydrogen or straight or branched alkyl (C1-C6);
n is an integer of 2 or 3;
A is NR^{10}, where R^{10} is hydrogen or straight or branched alkyl (C1-C6);
R^4 and R^5 may independently or simultaneously, be

a) hydrogen,
b) straight or branched alkyl (C1-C8) which may be substituted by

i) phenyl, or phenyl substituted by hydroxy or alkoxy (C1-C2),
ii) cycloalkyl (C5-C6).
iii) alkylthio (C1-C6),
iv) carboxamido,
v) straight or branched alkoxy (C1-C6) which may be substituted by phenyl,

c) phenyl, or
d) cycloalkyl (C3-C7), which may be substituted by straight or branched alkyl (C1-C6),

in addition, R^4 and R^5, taken together can be

$$-(CH_2)_r-$$

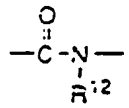
where

r is an integer of 4 or 5;

G is one of the following fragments

$$-HC=CH-,\ -CH_2-CH_2-,\ \text{or}\ -CH_2-$$

or the following fragment



where R^{12} is hydrogen or methyl, such that the carbonyl group is attached to the carbon bearing R^4 and R^5 and that NR^{12} is connected to R^6;
p is an integer of 0 or 1;
R^6 is

a) hydrogen,
b) straight or branched alkyl (C1-C6) which may be substituted by

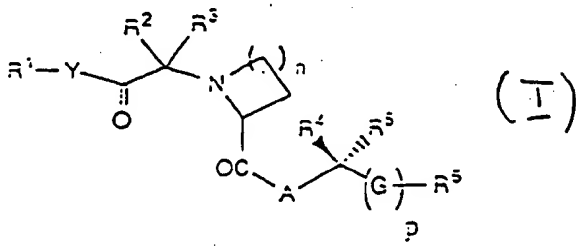
i) phenyl,
ii) phenyl substituted with straight or branched alkyl (C1-C6), straight or branched alkoxy (C1-C6), or
iii) pyridyl, or

c) phenyl, naphthyl, furyl, thiofuryl, cycloalkyl (C5-C8), bicycloalkyl (C6-C10), tricycloalkyl (C7-C12), tetracycloalkyl (C10-C16), pentacycloalkyl (C11-C20) or benzoyl, such groups may be substituted by

i) an amine,
ii) amino substituted by a straight or branched alkoxycarbonyl (C1-C6) that may be substituted by phenyl or an alkene (C2-C6),
iii) amino substituted by alkanoyl (C1-C6), or benzoyl,
iv) sulfonamide ($-SO_2NH_2$), or
v) hydroxy, or a straight or branched alkoxy (C1-C6), that may be substituted by phenyl;

and pharmaceutically acceptable salts thereof.

2. A compound of formula (I) according to claim 1



(I)

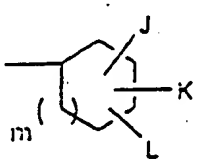
wherein

R^1 is

a) hydrogen,
b) linear or branched alkyl (C1-C6) which may be substituted

i) once by hydroxy,
ii) once by phenyl which may be substituted by straight or branched alkyl (C1-C4), or straight or branched alkoxy (C1-C6),
iii) once by cycloalkyl (C3-C8) which may be substituted by straight or branched alkyl (C1-C6), or straight or branched alkoxy (C1-C4),
iv) once by bicycloalkyl (C6-C10) which may be substituted by straight or branched alkyl (C1-C8), or straight or branched alkoxy (C1-C4),
v) once by tricycloalkyl (C7-C12) which may be substituted by straight or branched alkyl (C1-C6), or straight or branched alkoxy (C1-C4),
vi) once by tetracycloalkyl (C10-C12), which may be substituted by straight or branched alkyl (C1-C8), or straight or branched alkoxy (C1-C4),
vii) up to two times by phenyl and cycloalkyl (C5-C7), or
viii) up to two times by phenyl and morpholinyl,

c) alkene (C3-C8), which may be substituted by phenyl, straight or branched alkyl (C1-C4), or straight or branched alkoxy (C1-C4),
d) diene (C4-C7) substituted by straight or branched alkyl (C1-C6), or straight or branched alkoxy (C1-C4),
e) triene (C10-C16) substituted up to three times by straight or branched alkyl (C1-C6), or straight or branched alkoxy (C1-C4), or
f) cycloalkyl (C5-C10), or the cycloalkyl fragment



where

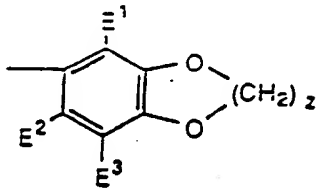
m is an integer of 0, 1, or 2,
J, K, and L are independently or simultaneously

i) hydrogen,
ii) straight or branched alkyl (C1-C5), which may be substituted by phenyl, or straight or branched alkoxy (C1-C4),
iii) phenyl, or
iv) phenyl substituted by straight or branched alkyl (C1-C4), or chlorine, or straight or branched alkoxy (C1-C4),

g) bicycloalkyl (C7-10) which may be substituted up to 3 times with straight or branched alkyl (C1-C6), or straight or branched alkoxy (C1-C4),
h) tricycloalkyl (C7-14) which may be substituted up to 3 times with straight or branched alkyl (C1-C6), or straight or branched alkoxy (C1-C4),
i) tetracycloalkyl (C10-C15) which may be substituted up to 3 times by straight or branched alkyl (C1-C6), or straight or branched alkoxy (C1-C4),
j) naphthyl derivatives, or the heteroaryl derivatives benzothienyl, benzofuryl, benzopyranyl, furyl, pyridyl, pyranyl, or 1,3-oxazolyl, said derivatives may be substituted up to two times by

i) straight or branched alkyl (C1-C6),
ii) halogen,
iii) or both:

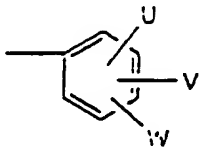
k) 1,2,3,4-tetrahydronaphthyl,
l) the piperonyl fragment



where

z is an integer of 1, or 2,
and E^1, E^2, and E^3 can be independently or simultaneously hydrogen, straight or branched alkyl (C1-C4), straight or branched alkoxy (C1-C4), or chlorine,

m) the aryl derivative



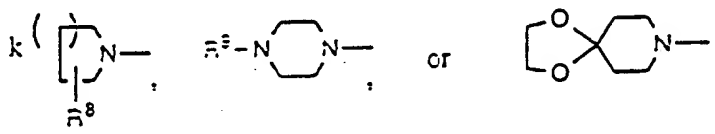
where

U, V, and W can be independently or simultaneously

i) hydrogen,
ii) straight or branched alkyl (C1-C4), which may b substituted by phenyl,

iii) straight or branched alkoxy (C1-C6), which may be substituted by phenyl, straight or branched alkoxy (C1-C4), or phenoxy,
iv) hydroxy,
v) phenyl,
vi) halogen,
vii) nitro,
viii) benzoyl, or
ix) phenoxy;

Y is a covalent bond, oxygen, NR^7, where R^7 is hydrogen,
in addition,
R^1-Y- may also be



where

k is an integer of 1, or 2,
R^8 is

a) hydrogen,
b) carboalkoxy with a straight or branched alkoxy (C1-C4),
c) straight or branched alkyl (C1-C4) which may be substituted by phenyl, or straight or branched alkoxy (C1-C4), or
d) phenyl, or phenyl substituted by halogen,

R^9 is phenyl which may be substituted by alkyl (C1-C4);
R^2 and R^3 are defined as follows: one of R^2 and R^3 are hydrogen, and the other is hydrogen or straight or branched alkyl (C1-C6);
n is an integer of 2 or 3;
A is NR^{10}, where R^{10} is hydrogen or straight or branched alkyl (C1-C4);
R^4 is

a) hydrogen,
b) straight or branched alkyl (C1-C6) which may be substituted by

i) phenyl, or phenyl substituted by hydroxy or methoxy,
ii) cycloalkyl (C5-C6),
iii) alkylthio (C1-C6),
iv) carboxamido, or
v) straight or branched alkoxy (C1-C6) which may be substituted by phenyl,

c) phenyl, or
d) cycloalkyl (C3-C7), which may be substituted by straight or branched alkyl (C1-C6);

R^5 is hydrogen or straight or branched alkyl (C1-C4), and R^4 and R^5, taken together can be

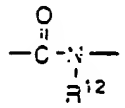
$$-(CH_2)_r-$$

where r is an integer of 4 or 5;

G is one of the following fragments

-HC=CH-, $-CH_2-CH_2-$, or $-CH_2-$

or the following fragment



where the carbonyl group is attached to the carbon bearing R^4 and R^5 and NR^{12} is connected to R^6, R^{12} is hydrogen or methyl;

p is an integer of 0 or 1;
R^6 is

a) hydrogen,
b) straight or branched alkyl (C1-C4) which may be substituted by

i) phenyl,
ii) phenyl substituted with straight or branched alkyl (C1-C4), straight or branched alkoxy (C1-C4), or
iii) 2- or 4-pyridyl,

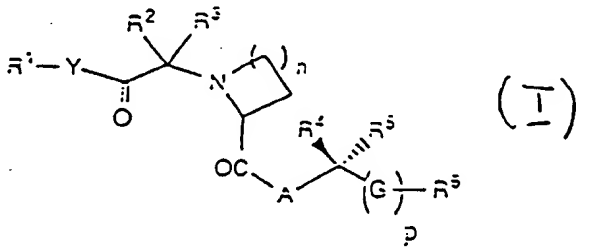
c) phenyl or naphthyl, which may be substituted by

i) amine,
ii) amino substituted by a straight or branched alkoxycarbonyl (C1-C6) that may be substituted by phenyl or an alkene (C2-C6),
iii) amino substituted by alkanoyl (C1-C6), or benzoyl,
iv) sulfonamide ($-SO_2NH_2$), or
v) straight or branched alkoxy (C1-C6), that may be substituted by phenyl,

d) benzoyl,
e) furyl, or thiofuryl, or
f) cycloalkyl (C5-C8), bicycloalkyl (C6-C10), tricycloalkyl (C7-C12), or tetracycloalkyl (C10-C14);

and pharmaceutically acceptable salts thereof.

3. A compound of formula (I) according to claim 1



(I)

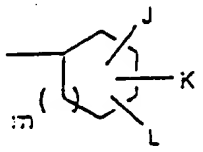
wherein

R^1 is

a) hydrogen,
b) linear or branched alkyl (C1-C6) which may be substituted by

i) hydroxy,
ii) phenyl, or phenyl substituted by straight or branched alkyl (C1-C4),
iii) cycloalkyl (C3-C8) which may be substituted by straight or branched alkyl (C1-C4),
iv) bicycloalkyl (C6-C9) which may be substituted by straight or branched alkyl (C1-C6),
v) tricycloalkyl (C7-C12) which may be substituted by straight or branched alkyl (C1-C4),
vi) tetracycloalkyl (C10-C12), which may be substituted by straight or branched alkyl (C1-C6),
vii) both phenyl and cycloalkyl (C5-C6), or
viii) both phenyl and morpholinyl,

c) alkene (C3-C6), which may be substituted by phenyl,
d) diene (C5-C6) substituted by straight or branched alkyl (C1-C4),
e) triene (C13-C16) substituted up to three times by straight or branched alkyl (C1-C4),
f) cycloalkyl (C5-C6), or the cycloalkyl fragment



where

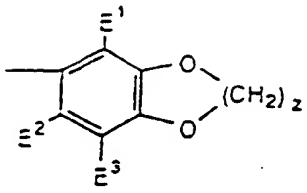
m is an integer of 0, 1, or 2,
J, K, and L are independently or simultaneously,

i) hydrogen,
ii) straight or branched alkyl (C1-C5),
iii) phenyl, or
iv) phenyl substituted by straight or branched alkyl (C1-C4), or chlorine, or straight or branched alkoxy (C1-C4),

g) bicycloalkyl (C7-8) which may be substituted up to 3 times with straight or branched alkyl (C1-C4),
h) tricycloalkyl (C7-C12) which may be substituted up to 2 times with straight or branched alkyl (C1-C6),
i) tetracycloalkyl (C10-C12), which may be substituted up to 3 times by straight or branched alkyl (C1-C4),
j) 2-benzothienyl substituted independently or simultaneously at least twice by either

i) straight or branched alkyl (C1-C3),
ii) chlorine,
iii) or both,

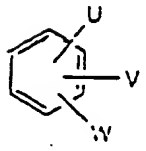
k) 2-furyl,
l) 2-pyridyl,
m) 2-naphthyl,
n) 1,2,3,4-tetrahydronaphthyl,
o) 2-benzopyranyl,
p) 2-benzofuryl,
q) the piperonyl fragment



where

z is an integer of 1, or 2,
and E^1, E^2, and E^3 are hydrogen, or

r) the aryl derivative

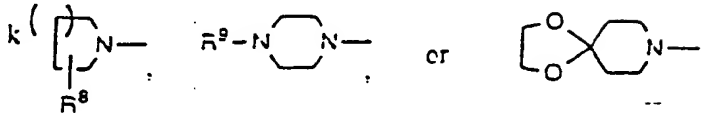


where

U, V, and W can be independently or simultaneously

i) hydrogen,
i) straight or branched alkyl (C1-C4),
ii) straight or branched alkoxy (C1-C4),
iii) alkoxy (C2) substituted by alkoxy (C2), or phenoxy,
iv) hydroxy,
v) phenyl,
vi) fluorine,
vii) chlorine,
viii) bromine,
ix) nitro,
x) benzyloxy,
xi) benzoyl,
xii) phenoxy;

Y is a covalent bond, oxygen, NR^7, where R^7 is hydrogen;
in addition,
R^1-Y- may also be



where

k is an integer of 1, or 2,
R^8 is

a) hydrogen,
b) carboalkoxy with alkoxy (C1-C2),
c) straight or branched alkyl (C1-C4) which may be substituted by phenyl,
d) phenyl,

R^9 is phenyl;
R^2 and R^3 are defined as follows: one of R^2 and R^3 is hydrogen, and the other is hydrogen or straight or branched alkyl (C1-C4);
n is an integer of 2 or 3;
A is NR^{10}, where R^{10} is hydrogen or methyl;
R^4 is

a) hydrogen,
b) straight or branched alkyl (C1-C4) which may be substituted by

i) phenyl,
ii) cycloalkyl (C5-C6),
iii) alkylthio (C1-C4),
iv) carboxamido, or
v) benzyloxy, or

c) phenyl;

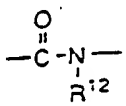
R^5 is hydrogen or straight or branched alkyl (C1-C4), and R^4 and R^5, taken together can be

$$-(CH_2)_r--$$

where r is integer 5;
G is one of the following fragments

$$-HC{=}CH-,\ -CH_2{\cdot}CH_2-,\ \text{or}\ -CH_2-$$

or the following fragment



where the carbonyl group is attached to the carbon bearing R^4 and R^5 and NR^{12} is connected to R^6,
R^{12} is hydrogen or methyl;
p is an integer of 0 or 1;
R^6 is

a) hydrogen,
b) straight or branched alkyl (C1-C4) which may be substituted by

i) phenyl,
ii) phenyl substituted with alkoxy (C1-C2),
iii) 2- or 4-pyridyl,

c) phenyl which may be substituted by

i) amino,
ii) amino substituted by allyloxycarbonyl,

iii) amino substituted by acetyl,
iv) amino substituted by benzoyl,
v) amino substituted by benzyloxycarbonyl,
iii) sulfonamide ($-SO_2NH_2$), or
iv) straight or branched alkoxy (C1-C4),

d) benzoyl,
e) furyl,
f) naphthyl,
g) cycloalkyl (C5-C8), or
h) tetracycloalkyl (C10-C12);

and pharmaceutically acceptable salts thereof.

4. A compound according to claims 1-3 selected from the group consisting of:

L-Isoleucine, N-[1-(2-Benzyloxy-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-Methoxy-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-Phenyl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-Naphth-2-yl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-isoleucine, N-[1-(2-(Biphenyl-4-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(2-Methoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(5-Chloro-3-Methyl-benzo[B]thiophene-2-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(trans,trans-Hexa-2,4-dienyl-1-oxy)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(4-Chlorophenyl)-2-Oxoethyl])-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(4-Methylphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(4-Methoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-Methyl-N-[1-(2-Phenyl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-Phenyl-2-Oxoethyl)-L-Homoproline] Benzylamide;
L-Phenylglycine, N-[1-(2-Phenyl-2-Oxoethyl)-L-Proline Benzylamide;
L-Isoleucine, N-[1-(1-Methyl-2-Phenyl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(3-Methoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(3,4-Dihydroxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-Methyl-N-[1-(2-Benzyloxy-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(Carbobenzyloxymethylene)-L-Homoproline Benzylamide;
L-Isoleucine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(Carbo-tert-Butoxymethylene)-L-Proline] Benzylamide;
L-Isoleucine, N-[1-(2-tert-Butyl-2-Oxoethyl)-L-Proline] Benzylamide;
L-Isoleucine, N[1-(2-(2,5-Dimethoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(2,4-Dimethoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(2-Nitrophenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(4-Nitrophenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(3-Benzyloxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(2,4-Dimethylphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(4-Fluorophenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(4-Bromophenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2,4-Dichlorophenylcarbamoylmethyl)-L-Proline] Benzylamide;
L-Isoleucine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Homoproline] Benzylamide;
L-Isoleucine, N-[1-(2-Furan-2-yl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-Pyrid-2-yl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(Adamant-1-ylcarbamoylmethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(cis-Octahydro-pentalen-1-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-[2-(2,6,6-Trimethyl-Bicyclo[3.1.1]hept-3-yl)-2-Oxoethyl]-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(4-Pentylcyclohexyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(1,2,3,4-tetrahydro-Napththalen-2-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isol ucin , N-[1-(2-(1-Methyl-Cycloh xyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isol ucin , N-[1-(2-Oxo-2-Tricyclo[3.3.1.0 ^{3,7}]Non-3-yl-Ethyl)-L-Prolyl] Benzylamid ;
L-Isol ucine, N-[1-(2-Oxo-3-(3-Methyl-Adamantan-1-yl)-Propyl)-L-Pr lyl] Benzylamide;

L-Proline, 1-(2-Adamantan-1-yl-2-Oxoethyl) Benzyl Ester;
L-Isoleucine, N-[1-(2-(Biphenyl-4-yl)-2-Oxoethyl)-L-Prolyl] 1,2,3,4-Tetrahydroisoquinolinamide;
L-Isoleucine, N-[1-(2-(Biphenyl-4-yl)-2-Oxoethyl)-L-Prolyl] Benzyl Ester;
L-Isoleucine, N-[1-(2-(Biphenyl-4-yl)-2-Oxoethyl)-L-Prolyl] tert-Butylamide;
L-Phenylalanine, N-[1-(2-(Biphenyl-4-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Methionine, N-[1-(2-(Biphenyl-4-yl])-2-Oxoethyl)-L Prolyl] Benzylamide;
Glycine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Valine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Leucine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Phenylalanine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Norvaline, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Norleucine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Asparagine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Serine-(O-Benzyl Ether), N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-β-Phenylalanine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Cyclohexylalanine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] alpha-(S)-methylbenzylamide;
L-Isoleucine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] alpha-(R)-methylbenzylamide;
L-Isoleucine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Pyridin-4-ylmethylamide;
L-Isoleucine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] Pyridin-2-ylmethylamide;
L-Isoleucine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] 4-methoxybenzylamide;
L-Isoleucine, N-[1-(2-Adamantan-1-yl-2-Oxoethyl)-L-Prolyl] 2-methoxybenzylamide;
L-Isoleucine, N-[1-(Carboxymetyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-[2-[N-(Piperidine-3-Carboxyic Acid Ethyl Ester)]-2-Oxoethyl]-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-[2-(N-4-Benzylpiperidyl))-2-Oxoethyl]-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-[2-(2-Methylpiperidine)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(2-Hydroxyethylamine)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-[2-(4-Phenylpiperazine)-2-Oxoethyl]-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-[2-(1-Pyrrolidine)-2-Oxoethyl]-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-[2-(N-Cyclopentylamino)-2-Oxoethyl]-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-[2-(N-(Phenylmethylamino))-2-Oxoethyl]-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(N-(Cyclohexylmethylamino))-2-Oxoethyl]-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(4-Phenylpiperazine)-2-Oxoethyl]-L-Prolyl] Benzylamide;
L-Isoleucine, N[1-(2-[1-(3,7,11-Trimethyldodeca-2,6,10-trien-1-ol)]-2-Oxoethyl)-L-Proline] Benzylamide;
L-Isoleucine, N-[1-(2-(3-Phenyl-2-Propen-1-Oxy)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(3-Phenyl-3-Methyl-2-Propen-1-Oxy)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(1-Phenylpropoxy)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(1-Phenyl-1-Cyclohexylmethoxy)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(1-Phenyl-2-(4-Morpholino)Ethoxy)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(2-Oxy-2-Methyladamant-2-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(Adamantan-2-ylcarbamoylmethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(Adamant-1-ylmethylcarbamoylmethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(2-Methyl-1-(S)-Phenyl-1-Propoxy)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(2-Methyl-1-(R)-Phenyl-1-Propoxy)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(4-tert-Butylcyclohexyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-Bicyclo[2.2.1]hept-2-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(Chroman-2-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide Hydrochloride Salt;
L-Isoleucine, N-[1-(2-(Benzofuran-2-yl)-2-Oxoethyl)-L-Prolyl] Benzylamide Hydrochloride Salt;
L-Isoleucine, N-[1-(2-(3-Benzoyloxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(4-Benzoyloxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(2-Benzoyloxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(3-Phenoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(2-Phenoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(3,4,5-Triethoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamid ;
L-Isol ucine, N-[1-(2-(Benzo[1,3]dioxol-5-yl)-2-Oxoethyl)-L-Prolyl] Benzylamid ;
L-Isol ucine, N-[1-(2-Oxo-2-[4-(2-Phenoxyethoxy)-Phenyl]-Ethyl)-L-Prolyl] Benzylamide;

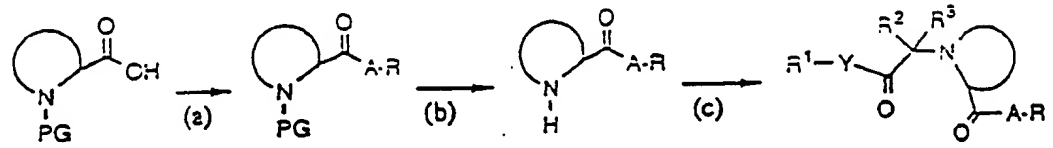
L-Isoleucine, N-[1-(2-(4-Phenoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(2,4,6-Trimethoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(2,3-Dimethoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(2,6-Dimethoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(1-(4-Methylphenyl)cyclohexyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(1-(4-Chlorophenyl)cyclohexyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(2,3,4-Trimethoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(1-Phenylcyclohexyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
L-Isoleucine, N-[1-(2-(2,4,5-Trimethoxyphenyl)-2-Oxoethyl)-L-Prolyl] Benzylamide;
1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] L-Proline Benzyl Ester Hydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] Benzylamide Hydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-Phenethylamide Hydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 3-Phenylpropylamide Hydrochloride;
L-Proline, 1-[2,(3,4,5-Trimethoxyphenyl)-2-Oxoethyl) 4-Phenylbutylamide Hydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-(Pyrid-2-yl)ethylamide Dihydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl) 2-(4-aminophenyl)ethylamide Dihydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 3-(4-[N-Carballyloxy]aminophenyl)propyl Ester Hydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-Phenyl-2-oxoethylamide;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] Tetrahydrofurfurylamide;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] Naphthalen-1-ylmethylamide;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-(4-Sulfamoylphenyl)ethylamide;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 4-Phenylpiperidenylamide;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 4-Methoxybenzamide Hydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 3-Methoxybenzamide Hydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-Methoxybenzamide Hydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] N-Methylphenethylamide Hydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] (S)-α-methylbenzylamide Hydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl)] (R)-α-methylbenzylamide Hydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 1-methyl-3-phenylpropylamide Hydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] Adamant-1-ylmethylamide Hydrochloride;
L-Proline 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl) 1-(R)-(1-naphthyl)ethylamide Hydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] Cyclohexylmethylamide;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] Diphenylmethylamide Hydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] tert-Butylamide Hydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 1,2-Diphenylethylamide Hydrochloride;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] Cyclohexyl amide Hydrochloride;
1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] L-Homoproline Benzyl Ester Hydrochloride;
L-Homoproline, 1-[2-(3,4,5,Trimethoxyphenyl)-2-Oxoethyl] Benzylamide Hydrochloride;
L-Homoproline 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] Adamant-1-ylmethylamide Hydrochloride;
L-Homoproline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] tetrahydrofurfurylamide;
L-Homoproline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-(4-Sulfamoylphenyl)ethylamide;
L-Homoproline, 1-[2-(3,4,5,Trimethoxyphenyl)-2-Oxoethyl] (S)-α-methylbenzylamide Hydrochloride;
L-Homoproline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] (1-(S)-[2'-(S)-methylpropyl]-3-phenylprop-2-Eenyl)-amide;
L-Homoproline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] (1-(S)-[2'-(S)-methylpropyl]-3-phenylpropyl)-amide;
L-Isoleucine, N-[1-(2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl)-L-Homoprolyl] Benzylamide;
L-Proline 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-(4-(N-Acetyl)aminophenyl)ethylamide;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-(4-(N-Benzoyl)aminophenyl)ethylamide;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-(4-(N-carboalloxy)aminophenyl)ethylamide;
L-Proline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 2-(4-(N-Carbobenzyloxy)aminophenyl)ethylamide;
L-Homoproline, 1-[2-(3,4,5-Trimethoxyphenyl)-2-Oxoethyl] 3-(4-(N-Carboallyloxy)aminophenyl)propyl Ester Hydrochloride;
L-Proline, 1-[2-Adamantan-1-yl-2-Oxoethyl] 3-(4-(N-Carboallyloxy) aminophenyl)propyl Ester Hydrochloride; and
L-Homoproline, 1-[2-Adamant-1-yl-2-Oxoethyl] 3-(4-(N-Carboallyloxy)aminophenyl)propyl Est r Hydrochlorid .

5. A compound according to claims 1 to 4 for the treatment of inflammations.

6. A medicament containing at least one compound according to claims 1 to 4.

7. Use of the compounds according to claims 1 to 4 for the manufacturing of a composition for the treatment of inflammation.

8. A method for making the compounds of claims 1 to 4, comprising the following steps:



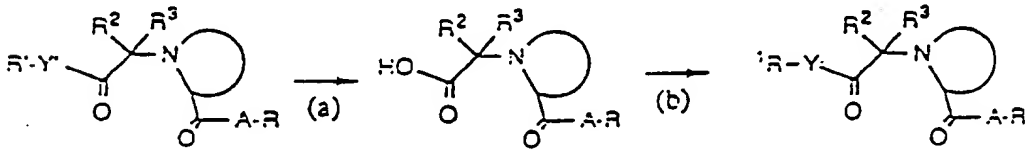
which are

(a) coupling an N-protected imino acid to an amine or an alcohol to form a C-substituted, N-protected imino acid;

(b) removing the protecting group from said C-substituted, N-protected imino acid; and

(c) alkylating the resulting imino acid from step (b) at the nitrogen position with an α-halo ester, α-halo ketone, or an α-halo amide.

9. A method for making the compounds of claims 1 to 4, comprising the following steps:

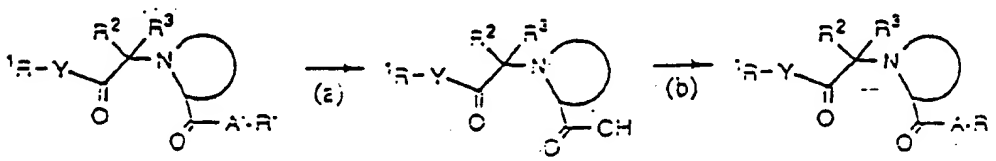


which are

a) deprotecting the 2-position of a first 2-oxoethyl derivative; and

b) coupling the resulting acid derivative from step (a) to form a second 2-oxoethyl derivative.

10. A method for making the compounds of claims 1 to 4 comprising the following steps:



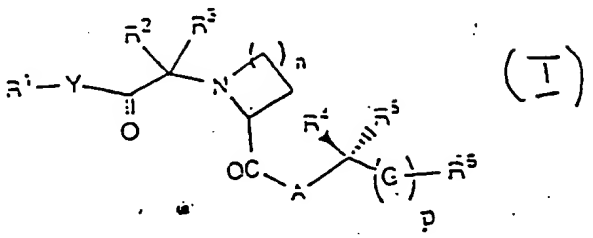
which ar

a) deprot cting the imino acid C-termini of a 2-oxoethyl derivative to form a 2-oxoethyl imino acid; and

b) coupling said 2-oxoethyl imino acid resulting from step (a) with an amine or an alcohol to form a C-substituted, 2-oxoethyl imino acid derivative.

Patentansprüche

1. Verbindung der folgenden Struktur:



worin gilt:

R^1 ist:

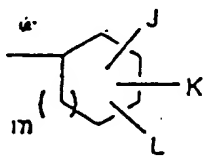
a) Wasserstoff,
b) ein linearer oder verzweigter C1-8-Alkylrest, der unabhängig oder gleichzeitig substituiert sein kann, und zwar bis zu 2 Mal mit einem:

i) Hydroxyrest,
ii) Phenylrest, der mit einem geradkettigen oder verzweigten C1-8-Alkyl- oder einem geradkettigen oder verzweigten C1-6-Alkoxyrest substituiert sein kann,
iii) C3-10-Cycloalkylrest, der mit einem geradkettigen oder verzweigten C1-8-Alkyl- oder einem geradkettigen oder verzweigten C1-6-Alkoxyrest substituiert sein kann,
iv) C6-12-Bicycloalkylrest, der mit einem geradkettigen oder verzweigten C1-10-Alkyl- oder einem geradkettigen oder verzweigten C1-6-Alkoxyrest substituiert sein kann,
v) C7-14-Tricycloalkylrest, der mit einem geradkettigen oder verzweigten C1-8-Alkyl- oder einem geradkettigen oder verwzeigten C1-6-Alkoxyrest substituiert sein kann,
vi) C10-14-Tetracycloalkylrest, der mit einem geradkettigen oder verzweigten C1-8-Alkyl- oder einem geradkettigen oder verzweigten C1-6-Alkoxyrest substituiert sein kann, oder mit einem
vii) Morpholinylrest,

c) ein C3-10-Alken-, C4-10-Dien- oder ein C8-18-Trienrest, die unabhängig voneinander oder gleichzeitig substituiert sein können, und zwar bis zu 3 Mal mit einem:

i) Phenyl-,
ii) geradkettigen oder verzweigten C1-6-Alkyl- oder mit einem
iii) geradkettigen oder verzweigten C1-6-Alkoxyrest,

d) ein C5-10-Cycloalkylrest oder das Cycloalkyl-Fragment:



worin gilt:

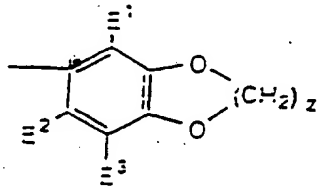
m ist eine ganze Zahl von 0, 1 oder 2,
J, K und L sind unabhängig voneinander oder gleichzeitig:

i) Wasserstoff,
ii) ein geradkettiger oder verzweigter C1-5-Alkylrest, der mit einem Phenyl- oder einem geradkettigen oder verzweigten C1-6-Alkoxyrest substituiert sein kann,
iii) ein geradkettiger oder verzweigter C1-5-Alkoxy-, iii) Phenyl- oder ein
iv) Phenylrest, der mit einem geradkettigen oder verzweigten C1-6-Alkylrest oder mit Chlor oder mit einem geradkettigen oder verzweigten C1-6-Alkoxyrest substituiert ist,

e) ein C7-10-Bicycloalkyl-, C7-14-Tricycloalkyl-, C10-16-Tetracycloalkyl- oder ein C11-20-Pentacycloalkylrest, welche, unabhängig voneinander oder gleichzeitig, bis zu Mal mit einem geradkettigen oder verzweigten C1-6-Alkyl- oder einem geradkettigen oder verzweigten C1-6-Alkoxy- oder einem Phenylrest substituiert sein können,
f) die Aryl-Derivate Tetrahydronaphthyl, Benzothienyl, Benzofuryl, Benzopyranyl, Furyl, Pyridyl, Pyranyl, 1,3-Oxazolyl oder Naphthyl, wobei die genannten Aryl-Derivate, unabhängig voneinander oder gleichzeitig, bis zu 2 Mal substituiert sein können mit:

i) einem geradkettigen oder verzweigten C1-6-Alkylrest,
ii) einem geradkettigen oder verzweigten C1-6-Alkoxyrest,
iii) Halogen, wobei Halogen Fluor, Chlor, Brom oder Jod ist,

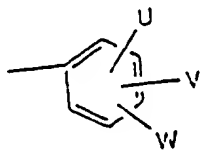
g) das Piperonyl-Fragment:



worin gilt:

z ist eine ganze Zahl von 1 oder 2,
und E^1, E^2 und E^3 sind, unabhängig voneinander oder gleichzeitig, Wasserstoff, ein geradkettiger oder verzweigter C1-6-Alkyl- oder ein geradkettiger oder verzweigter C1-6-Alkoxyrest oder Chlor, oder

h) das Aryl-Derivat:



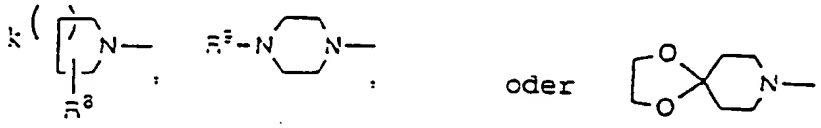
worin gilt:

U, V und W sind, unabhängig von inander oder gleichzeitig:

i) Wasserstoff,

ii) eine geradkettige oder verzweigte C1-6-Alkyl-, geradkettige oder verzweigte C1-6-Alkoxy-, Phenyl- oder eine Phenoxygruppe, wobei diese Gruppen mit einem Phenyl-, geradkettigen oder verzweigten C1-6-Alkoxy- oder einem Phenoxyrest substituiert sein können,
iii) ein Hydroxyrest,
iv) Halogen,
v) eine Nitrogruppe oder
vi) ein Benzoylrest;

Y ist eine kovalente Bindung, Sauerstoff oder NR^7, worin R^7 Wasserstoff ist,
ausserdem kann R^1-Y- auch sein:



worin gilt:

k ist eine ganze Zahl von 1 oder 2,
R^8 ist:

a) Wasserstoff,
b) ein Carboalkoxyrest mit einem geradkettigen oder verzweigten C1-6-Alkoxyrest,
c) ein geradkettiger oder verzweigter C1-6-Alkylrest, der mit einem Phenyl- oder einem geradkettigen oder verzweigten C1-6-Alkoxyrest substituiert sein kann,
d) ein Phenyl- oder ein Phenylrest, der mit Halogen substituiert ist,

R^9 ist ein Phenylrest, der mit einem geradkettigen oder verzweigten C1-6-Alkylrest substituiert sein kann;

R^2 und R^3 sind wie folgt definiert: einer der Reste R^2 und R^3 ist Wasserstoff, und der andere Rest ist Wasserstoff oder ein geradkettiger oder verzweigter C1-6-Alkylrest;
n ist eine ganze Zahl von 2 oder 3;
A ist NR^{10}, worin R^{10} Wasserstoff oder ein geradkettiger oder verzweigter C1-6-Alkylrest ist;
R^4 und R^5 sind, unabhängig voneinander oder gleichzeitig:

a) Wasserstoff,
b) ein geradkettiger oder verzweigter C1-8-Alkylrest, der substituiert sein kann mit einem:

i) Phenyl- oder einem mit einem Hydroxy- oder C1-2-Alkoxyrest substituierten Phenylrest,
ii) C5-6-Cycloalkyl-,
iii) C1-6-Alkylthio-,
iv) Carboxamido-,
v) geradkettigen oder verzweigten C1-6-Alkoxyrest, der mit einem Phenylrest substituiert sein kann,

c) ein Phenyl- oder
d) ein C3-7-Cycloalkylrest, der mit einem geradkettigen oder verzweigten C1-6-Alkylrest substituiert sein kann,

ausserdem können R^4 und R^5, zusammengenommen, sein:

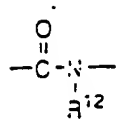
$$-(CH_2)_r-$$

worin gilt:

r ist eine ganze Zahl von 4 oder 5;
G ist eines der folgenden Fragmente:

$$-HC=CH-,\ -CH_2-CH_2-\text{ oder }-CH_2-$$

oder das folgende Fragment:



worin gilt:
R^{12} ist Wasserstoff oder ein Methylrest, wobei die Carbonylgruppe an den Kohlenstoff, der die Reste R^4 und R^5 aufweist, und NR^{12} an R^6 gebunden sind;
p ist eine ganze Zahl von 0 oder 1;
R^6 ist:

a) Wasserstoff,
b) ein geradkettiger oder verzweigter C1-6-Alkylrest, der substituiert sein kann mit einem:

i) Phenylrest,
ii) Phenylrest, der mit einem geradkettigen oder verzweigten C1-6-Alkyl- oder einem geradkettigen oder verzweigten C1-6-Alkoxyrest substituiert ist, oder mit einem
iii) Pyridylrest, oder

c) eine Phenyl-, Naphthyl-, Furyl-, Thiofuryl-, C5-6-Cycloalkyl-, C6-10-Bicycloalkyl-, C7-12-Tricycloalkyl-, C10-16-Tetracycloalkyl-, C11-20-Pentacycloalkyl- oder eine Benzoylgruppe, wobei diese Gruppen substituiert sein können mit:

i) einem Amin,
ii) einer Aminogruppe, die mit einem geradkettigen oder verzweigten C1-6-Alkoxycarbonylrest substituiert ist, der mit einem Phenyl- oder einem C2-6-Alkenrest substituiert sein kann,
iii) einer Aminogruppe, die mit einem C1-6-Alkanoyl- oder einem Benzoylrest substituiert ist,
iv) Sufonamid($-SO_2NH_2$) oder mit einem
v) Hydroxy- oder einem geradkettigen oder verzweigten C1-6-Alkoxyrest, der mit einem Phenylrest substituiert sein kann;

sowie pharmazeutisch geeignete Salze davon.

2. Verbindung der Formel (I) gemäß Anspruch 1,
worin gilt:

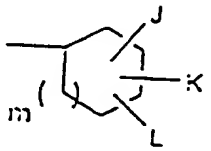
R^1 ist:

a) Wasserstoff,
b) lineares oder verzweigtes C1-6-Alkyl, das substituiert sein kann:

i) 1 Mal mit einem Hydroxyrest,
ii) 1 Mal mit Phenyl, das mit einem geradkettigen oder verzweigten C1-4-Alkyl oder einem geradkettigen oder verzweigten C1-6-Alkoxy substituiert sein kann,
iii) 1 Mal mit C3-8-Cycloalkyl, das mit inem geradkettigen oder verzweigten C1-6-Alkyl oder einem geradkettig n oder verzweigten C1-4-Alkoxy substituiert sein kann,
iv) 1 Mal mit C6-10-Bicycloalkyl, das mit einem geradkettigen oder verzweigten C1-8-Alkyl oder einem g radkettigen oder verzweigten C1-4-Alkoxy substituiert sein kann,

v) 1 Mal mit C7-12-Tricycloalkyl, das mit einem geradkettigen oder verzweigten C1-6-Alkyl oder einem geradkettigen oder verzweigten C1-4-Alkoxy substituiert sein kann,
vi) 1 Mal mit C10-12-Tetracycloalkyl, das mit einem geradkettigen oder verzweigten C1-8-Alkyl oder einem geradkettigen oder verzweigten C1-4-Alkoxy substituiert sein kann,
vii) bis zu 2 Mal mit Phenyl und C6-7-Cycloalkyl oder
viii) bis zu 2 Mal mit einem Phenyl- und einem Morpholinylrest,

c) C3-8-Alken, das mit Phenyl, geradkettigem oder verzweigten C1-4-Alkyl- oder geradkettigem oder verzweigten C1-4-Alkoxy substituiert sein kann,
d) C4-7-Dien, das mit geradkettigem oder verzweigten C1-6-Alkyl oder geradkettigem oder verzweigten C1-4-Alkoxy substituiert sein kann,
e) C10-16-Trien, das bis zu 3 Mal mit geradkettigem oder verzweigten C1-6-Alkyl oder geradkettigem oder verzweigten C1-4-Alkoxy substituiert sein kann, oder
f) C5-10-Cycloalkyl oder das Cycloalkyl-Fragment:



worin gilt:

m ist eine ganze Zahl von 0, 1 oder 2,
J, K und L sind, unabhängig voneinander oder gleichzeitig:

i) Wasserstoff,
ii) geradkettiges oder verzweigtes C1-5-Alkyl, das mit Phenyl oder geradkettigem oder verzweigten C1-4-Alkoxy substituiert sein kann,
iii) Phenyl oder
iv) Phenyl, substituiert mit geradkettigem oder verzweigten C1-4-Alkyl oder mit Chlor oder mit geradkettigem oder verzweigten C1-4-Alkoxy,

g) C7-10-Bicycloalkyl, das bis zu 3 Mal mit geradkettigem oder verzweigten C1-6-Alkyl oder geradkettigem oder verzweigten C1-4-Alkoxy substituiert sein kann,
h) C7-14-Tricycloalkyl, das bis zu 3 Mal mit geradkettigem oder verzweigten C1-6-Alkyl oder mit geradkettigem oder verzweigten C1-4-Alkoxy substituiert sein kann,
i) C10-15-Tetracycloalkyl, das bis zu 3 Mal mit geradkettigem oder verzweigten C1-6-Alkyl oder mit geradkettigem oder verzweigten C1-4-Alkoxy substituiert sein kann,
j) Naphthyl-Derivate oder die Heteroaryl-Derivate Benzothienyl, Benzofuryl, Benzopyranyl, Furyl, Pyridyl, Pyranyl oder 1,3-Oxazolyl, wobei die genannten Derivate bis zu 2 Mal substituiert sein können mit:

i) geradkettigem oder verzweigten C1-6-Alkyl,
ii) Halogen,
iii) oder mit beiden,

k) 1,2,3,4-Tetrahydronaphthyl,
l) das Piperonyl-Fragment:

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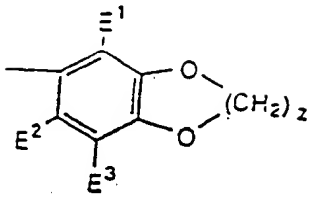
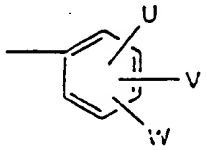


worin gilt:

z ist eine ganze Zahl von 1 oder 2,
und E^1, E^2 und E^3 sind, unabhängig voneinander oder gleichzeitig, Wasserstoff, geradkettiges oder verzweigtes C1-4-Alkyl, geradkettiges oder verzweigtes C1-4-Alkoxy oder Chlor,

m) das Aryl-Derivat:

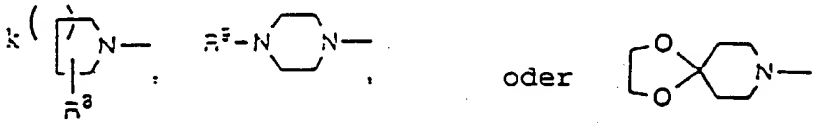


worin gilt:

U, V und W sind, unabhängig voneinander oder gleichzeitig:

i) Wasserstoff,
ii) geradkettiges oder verzweigtes C1-4-Alkyl, das mit Phenyl substituiert sein kann,
iii) geradkettiges oder verzweigtes C1-6-Alkoxy, das mit Phenyl, geradkettigem oder verzweigten C1-4-Alkoxy oder mit Phenoxy substituiert sein kann,
iv) Hydroxy,
v) Phenyl,
vi) Halogen,
vii) Nitro,
viii) Benzoyl oder
ix) Phenoxy;

Y ist eine kovalente Bindung, Sauerstoff oder NR^7, worin R^7 Wasserstoff ist,
ausserdem kann R^1-Y- auch sein:



worin gilt:

k ist eine ganze Zahl von 1 oder 2,
R^8 ist:

a) Wasserstoff,
b) Carboalkoxy mit einem geradkettigen oder verzweigten C1-4-Alkoxyrest,

c) geradkettiges oder verzweigtes C1-4-Alkyl, das mit Phenyl oder geradkettigem oder verzweigten C1-4-Alkoxy substituiert sein kann, oder
d) Phenyl oder mit Halogen substituiertes Phenyl,

R^9 ist Phenyl, das mit einem C1-4-Alkylrest substituiert sein kann;
R^2 und R^3 sind wie folgt definiert: einer der Reste R^2 und R^3 ist Wasserstoff, und der andere Rest ist Wasserstoff oder ein geradkettiger oder verzweigter C1-6-Alkylrest;
n ist eine ganze Zahl von 2 oder 3;
A ist NR^{10}, worin R^{10} Wasserstoff oder ein geradkettiger oder verzweigter C1-4-Alkylrest ist;
R^4 ist:

a) Wasserstoff,
b) geradkettiges oder verzweigtes C1-6-Alkyl, das substituiert sein kann mit:

i) Phenyl oder Phenyl, das mit einem Hydroxy- oder Methoxyrest substituiert ist,
ii) C5-6-Cycloalkyl,
iii) C1-6-Alkylthio,
iv) Carboxamido oder mit
v) geradkettigem oder verzweigten C1-6-Alkoxy, das mit einem Phenylrest substituiert sein kann,

c) Phenyl oder
d) C3-7-Cycloalkyl, das mit einem geradkettigen oder verzweigten C1-6-Alkylrest substituiert sein kann;

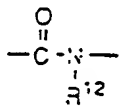
R^5 ist Wasserstoff oder geradkettiges oder verzweigtes C1-4-Alkyl, und R^4 und R^5 können, zusammengenommen, sein:

$$-(CH_2)_r-$$

worin r eine ganze Zahl von 4 oder 5 ist;
G ist eines der folgenden Fragmente:

$$-HC{=}CH-,\ -CH_2CH_2- \text{ oder } -CH_2-$$

oder das folgende Fragment:



worin die Carbonylgruppe an den die Reste R^4 und R^5 aufweisenden Kohlenstoff und NR^{12} an R^6 gebunden sind, und worin R^{12} Wasserstoff oder ein Methylrest ist;
p ist eine ganze Zahl von 0 oder 1;
R^6 ist:

a) Wasserstoff,
b) geradkettiges oder verzweigtes C1-4-Alkyl, das substituiert sein kann mit:

i) Phenyl,
ii) Phenyl, substituiert mit geradkettigem oder verzweigten C1-4-Alkyl oder mit geradkettigem oder verzweigten C1-4-Alkoxy, oder mit
iii) 2- oder 4-Pyridyl,

c) Phenyl oder Naphthyl, die substituiert sein können mit:

i) Amin,
ii) Amino, substituiert mit einem geradkettigen oder verzweigten C1-6-Alkoxycarbonylrest, der mit einem Phenyl- oder einem C2-6-Alkenrest substituiert sein kann,
iii) Amino, substituiert mit einem C1-6-Alkanoyl- oder einem Benzoylrest,
iv) Sulfonamid ($-SO_2NH_2$) oder mit
v) geradkettigem oder verzweigten C1-6-Alkoxy, das mit einem Phenylrest substituiert sein kann,

d) Benzoyl,
e) Furyl oder Thiofuryl oder
f) C5-8-Cycloalkyl, C6-10-Bicycloalkyl, C7-12-Tricycloalkyl oder C10-14-Tetracycloalkyl;

sowie pharmazeutisch geeignete Salze davon.

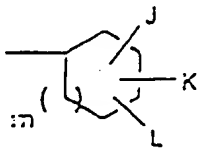
3. Verbindung der Formel (I) gemäß Anspruch 1, worin gilt:

R^1 ist:

a) Wasserstoff,
b) lineares oder verzweigtes C1-6-Alkyl, das substituiert sein kann mit:

i) Hydroxy,
ii) Phenyl oder Phenyl, substituiert mit geradkettigem oder verzweigten C1-4-Alkyl,
iii) C3-8-Cycloalkyl, das mit geradkettigem oder verzweigten C1-4-Alkyl substituiert sein kann,
iv) C6-9-Bicycloalkyl, das mit geradkettigem oder verzweigten C1-6-Alkyl substituiert sein kann,
v) C7-12-Tricycloalkyl, das mit geradkettigem oder verzweigten C1-4-Alkyl substituiert sein kann,
vi) C10-12-Tetracycloalkyl, das mit geradkettigem oder verzweigten C1-6-Alkyl substituiert sein kann,
vii) sowohl mit Phenyl als auch mit C5-6-Cycloalkyl oder
viii) sowohl mit Phenyl als auch mit Morpholinyl,

c) C3-6-Alken, das mit einem Phenylrest substituiert sein kann,
d) C5-6-Dien, das mit einem geradkettigen oder verzweigten C1-4-Alkylrest substituiert ist,
e) C13-16-Trien, substituiert bis zu 3 Mal mit geradkettigem oder verzweigten C1-4-Alkyl,
f) C5-6-Cycloalkyl oder das Cycloalkyl-Fragment:



worin gilt:

m ist eine ganze zahl von 0, 1 oder 2,
J, K und L sind, unabhängig voneinander oder gleichzeitig:

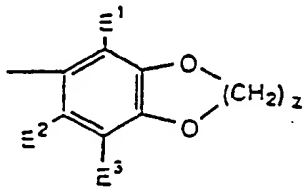
i) Wasserstoff,
ii) geradkettiges oder verzweigtes C1-5-Alkyl,
iii) Phenyl oder
iv) Phenyl, substituiert mit geradkettigem oder verzweigten C1-4-Alkyl oder mit Chlor oder mit geradkettigem oder verzweigten C1-4-Alkoxy,

g) C7-8-Bicycloalkyl, das bis zu 3 Mal mit geradkettigem oder verzweigten C1-4-Alkyl substituiert sein kann,
h) C7-12-Tricycloalkyl, das bis zu 2 Mal mit geradkettigem oder verzweigten C1-6-Alkyl substituiert sein kann,

i) C10-12-Tetracycloalkyl, das bis zu 3 Mal mit geradkettigem oder verzweigten C1-4-Alkyl substituiert sein kann,
j) 2-Benzothienyl, substituiert, unabhängig voneinander oder gleichzeitig, mindestens 2 Mal mit entweder:

i) geradkettigem oder verzweigten C1-3-Alkyl,
ii) Chlor
iii) oder mit beiden,

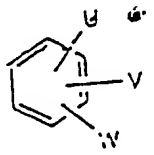
k) 2-Furyl,
l) 2-Pyridyl
m) 2-Naphthyl,
n) 1,2,3,4-Tetrahydronaphthyl,
o) 2-Benzopyranyl,
p) 2-Benzofuryl,
q) das Piperonyl-Fragment:



worin gilt:

z ist eine ganze Zahl von 1 oder 2, und E^1, E^2 und E^3 sind Wasserstoff, oder

r) das Aryl-Derivat:

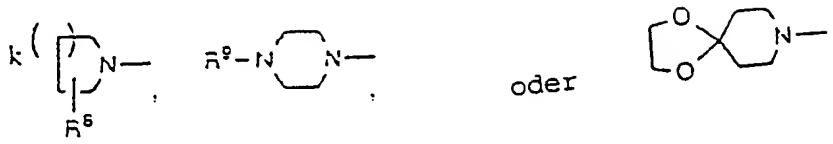


worin gilt:

U, V und W sind, unabhängig voneinander oder gleichzeitig

i) Wasserstoff,
ii) geradkettiges oder verzweigtes C1-4-Alkyl,
iii) geradkettiges oder verzweigtes C1-4-Alkoxy,
iv) C2-Alkoxy, substituiert mit C2-Alkoxy oder Phenoxy,
v) Hydroxy,
vi) Phenyl,
vii) Fluor,
viii) Chlor,
ix) Brom,
x) Nitro,
xi) Benzyloxy,
xii) Benzoyl,
xiii) Phenoxy;

Y ist eine kovalente Bindung, Sauerstoff oder NR^7, worin R^7 Wasserstoff ist, ausserdem kann R^1-Y- auch sein:



worin gilt:

k ist eine ganze Zahl von 1 oder 2,
R^8 ist:

a) Wasserstoff,
b) Carboalkoxy mit einem C1-2-Alkoxyrest,
c) geradkettiges oder verzweigtes C1-4-Alkyl, das mit einem Phenylrest substituiert sein kann,
d) Phenyl,

R^9 ist Phenyl;
R^2 und R^3 sind wie folgt definiert: einer der Reste R^2 und R^3 ist Wasserstoff, und der andere Rest ist Wasserstoff oder ein geradkettiger oder verzweigter C1-4-Alkylrest;
n ist eine ganze Zahl von 2 oder 3;
A ist NR^{10}, worin R^{10} Wasserstoff oder ein Methylrest ist; R^4 ist:

a) Wasserstoff,
b) geradkettiges oder verzweigtes C1-4-Alkyl, das substituiert sein kann mit:

i) Phenyl,
ii) C5-6-Cycloalkyl,
iii) C1-4-Alkylthio,
iv) Carboxamido oder mit
v) Benzyloxy, oder

c) Phenyl;

R^5 ist Wasserstoff oder ein geradkettiger oder verzweigter C1-4-Alkylrest, und R^4 und R^5 können, zusammengenommen, sein:

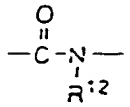
$$-(CH_2)_r-$$

worin r die Zahl 5 ist;

G ist eines der folgenden Fragmente:

$$-HC=CH-,\ -CH_2-CH_2-\text{ oder }-CH_2-$$

oder das folgende Fragment:



worin die Carbonylgruppe an den die Reste R^4 und R^5 aufweisenden Kohlenstoff und NR^{12} an R^6 gebunden sind, und worin

R^{12} Wasserstoff oder ein Methylrest ist;
p ist eine ganze Zahl von 0 oder 1;
R^6 ist:

a) Wasserstoff,
b) geradkettiges oder verzweigtes C1-4-Alkyl, das substituiert sein kann mit:

i) Phenyl,
ii) Phenyl, substituiert mit C1-2-Alkoxy,
iii) 2- oder 4-Pyridyl,

c) Phenyl, das substituiert sein kann mit:

i) Amino,
ii) Amino, substituiert mit Allyloxycarbonyl,
iii) Amino, substituiert mit Acetyl,
iv) Amino, substituiert mit Benzoyl,
v) Amino, substituiert mit Benzyloxycarbonyl
vi) Sulfonamid ($-SO_2NH_2$) oder mit
vii) geradkettigem oder verzweigten C1-4-Alkoxy,

d) Benzoyl,
e) Furyl,
f) Naphthyl,
g) C6-8-Cycloalkyl oder
h) C10-12-Tetracycloalkyl;

sowie pharmazeutisch geeignete Salze davon.

4. Verbindung gemäß einem der Ansprüche 1 bis 3, ausgewählt aus der Gruppe, bestehend aus:

L-Isoleucin-N-[1-(2-benzyloxy-2-oxoethyl)-L-prolyl]benzylamid;

L-Isoleucin-N-[1-(2-methoxy-2-oxoethyl)-L-prolyl]benzylamid;

L-Isoleucin-N-[1-(2-phenyl-2-oxoethyl)-L-prolyl]benzylamid;

L-Isoleucin-N-[1-(2-naphth-2-yl-2-oxoethyl)-L-prolyl]benzylamid;

L-Isoleucin-N-[1-(2-(biphenyl-4-yl)-2-oxoethyl)-L-prolyl]benzylamid;

L-Isoleucin-N-[1-(2-(2-methoxyphenyl)-2-oxoethyl)-L-prolyl]benzylamid;

L-Isoleucin-N-[1-(2-(5-chlor-3-methylbenzo[B]thiophen-2-yl)-2-oxoethyl)-L-prolyl]benzylamid;

L-Isoleucin-N-[1-(2-(trans,trans-h xa-2,4-dienyl-1-oxy)-2-oxoethyl)-L-prolyl]benzylamid;

L-Isoleucin-N-[1-(2-(4-chlorphenyl)-2-oxoethyl)-L-prolyl]benzylamid;

L-Isoleucin-N-[1-(2-(4-methylphenyl)-2-oxoethyl)-L-prolyl]benzylamid;

L-Isoleucin-N-[1-(2-(4-methoxyphenyl)-2-oxoethyl)-L-prolyl]benzylamid;

L-Isoleucin-N-methyl-N-[1-(2-phenyl-2-oxoethyl)-L-prolyl]benzylamid;

L-Isoleucin-N-[1-(2-phenyl-2-oxoethyl)-L-homoprolin]benzylamid;

L-Phenylglycin-N-[1-(2-phenyl-2-oxoethyl)-L-prolinbenzylamid

L-Isoleucin-N-[1-(1-methyl-2-phenyl-2-oxoethyl)-L-prolyl]benzylamid

L-Isoleucin-N-[1-(2-(3-methoxyphenyl)-2-oxoethyl)-L-prolyl]benzylamid

L-Isoleucin-N-[1-(2-(3,4-dihydroxyphenyl)-2-oxoethyl)-L-prolyl]benzyl-amid

L-Isoleucin-N-methyl-N-[1-(2-benzyloxy-2-oxoethyl)-L-prolyl]benzylamid

L-Isoleucin-N-[1-(carbobenzyloxymethylen)-L-homoprolin]benzylamid

L-Isoleucin-N-[1-(2-adamatan-1-yl-2-oxoethyl)-L-prolyl]benzylamid

L-Isoleucin-N-[1-(carbo-t-butoxymethylen)-L-prolin]benzylamid

L-Isoleucin-N-[1-(2-t-butyl-2-oxoethyl)-L-prolin]benzylamid

L-Isoleucin-N-[1-(2,5-dimethoxyphenyl)-2-oxoethyl)-L-prolyl]benzylamid

L-Isoleucin-N-[1-(2,4-dimethoxyhenyl)-2-oxoethyl)-L-prolyl]benzylamid

L-Isoleucin-N-[1-(2-(2-nitrophenyl)-2-oxoethyl)-L-prolyl]benzylamid

L-Isoleucin-N-[1-(2-(4-nitrophenyl)-2-oxoethyl)-L-prolyl]benzylamid

L-Isoleucin-N-[1-(2-(3-benzyloxyphenyl)-2-oxoethyl)-L-prolyl]benzyl-amid

L-Isoleucin-N-[1-(2-(2,4-dimethylphenyl)-2-oxoethyl)-L-prolyl]benzyl-amid

L-Isoleucin-N-[1-(2-(4-fluorphenyl)-2-oxoethyl)-L-prolyl]benzylamid

L-Isoleucin-N-[1-(2-(4-bromphenyl)-2-oxoethyl)-L-prolyl]benzylamid

L-Isoleucin-N-[1-(2,4-dichlorphenylcarbamoylmethyl)-L-prolyl]benzyl-amid

L-Isoleucin-N-[1-(2-adamatan-1-yl-2-oxoethyl)-L-homoprolin]benzylamid

L-Isoleucin-N-[1-(2-furan-2-yl-2-oxoethyl)-L-prolyl]benzylamid

L-Isoleucin-N-[1-(2-pyrid-2-yl-2-oxoethyl)-L-prolyl]benzylamid

L-Phenylalanin-N-[1-(2-(biphenyl-4-yl)-2-oxoethyl)-L-prolyl]benzylamid

L-Methionin-N-[1-(2-(biphenyl-4-yl)-2-oxoethyl)-L-Prolyl]benzylamid

Glycin-N-[1-(2-adamantan-1-yl-2-oxoethyl)-L-prolyl]benzylamid

L-Valin-N-[1-(2-adamantan-l-yl-2-oxoethyl)-L-prolyl]benzylamid

L-Leucin-N-[1-(2-adamantan-l-yl-2-oxoethyl)-L-prolyl]benzylamid

L-Phenylalanin-N-[1-(2-adamantan-1-yl-2-oxoethyl)-L-prolyl]benzylamid

L-Norvalin-N-[1-(2-adamantan-1-yl-2-oxoethyl)-L-prolyl]benzylamid

L-Norleucin-N-[1-(2-adamantan-1-yl-2-oxoethyl)-L-prolyl]benzylamid

L-Asparagin-N-[1-(2-adamantan-1-yl-2-oxoethyl)-L-prolyl]benzylamid

L-Serin-(O-benzylether)-N-[1-(2-adamantan-1-yl-2-oxoethyl)-L-prolyl]benzylamid

L-β-Phenylalanin-N-[1-(2-adamantan-1-yl-2-oxoethyl)-L-prolyl]benzylamid

L-Cyclohexylalanin-N-[1-(2-adamantan-1-yl-2-oxoethyl)-L-prolyl]benzylamid

L-Isoleucin-N-[1-(2-(4-benzoyloxyphenyl)-2-oxoethyl]-L-prolyl]benzylamid

L-Isoleucin-N-[1-(2-(2-benzoyloxyphenyl)-2-oxoethyl]-L-prolyl]benzylamid

L-Isoleucin-N-[1-(2-(3-phenoxyphenyl)-2-oxoethyl]-L-prolyl]benzylamid

L-Isoleucin-N-[1-(2-(2-phenoxyphenyl)-2-oxoethyl]-L-prolyl]benzylamid

L-Isoleucin-N-[1-(2-(3,4,5-triethoxyphenyl)-2-oxoethyl]-L-prolyl]benzylamid

L-Isoleucin-N-[1-(2-(benzo[1,3]dioxol-5-yl)-2-oxoethyl]-L-prolyl]benzylamid

L-Isoleucin-N-[1-{2-oxo-2-[4-(2-phenoxyethoxy)phenyl]ethyl}-L-prolyl]benzylamid

L-Isoleucin-N-[1-(2-(4-phenoxyphenyl)-2-oxoethyl)-L-prolyl]benzylamid

L-Isoleucin-N-[1-(2-(2,4,6-trimethoxyphenyl)-2-oxoethyl)-L-prolyl]benzylamid

L-Isoleucin-N-[1-(2-(2,3-dimethoxyphenyl)-2-oxoethyl)-L-prolyl]benzylamid

L-Isoleucin-N-[1-(2-(2,6-dimethoxyphenyl)-2-oxoethyl)-L-prolyl]benzylamid

L-Isoleucin-N-[1-(2-(1-(4-methylphenyl)cyclohexyl)-2-oxoethyl)-L-prolyl]benzylamid

L-Prolin-1-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-1-methyl-phenylpropylamid-Hydrochlorid

L-Prolin-1-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]adamant-1-ylmethylamid-Hydrochlorid

L-Prolin-1-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-1-(R)-(1-naphthyl)ethylamid-Hydrochlorid

L-Prolin-1-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]cyclohexylmethylamid

L-Prolin-1-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]diphenylmethylamid-Hydrochlorid

L-Prolin-1-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-t-butylamid-Hydrochlorid

L-Prolin-1-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-1,2-diphenylethylamid-Hydrochlorid

L-Prolin-1-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]cyclohexylamid-Hydrochlorid

1-[2-(3,4,5-Trim thoxyphenyl)-2-oxoethyl]-L-homoprolinbenzylest r-Hydrochlorid

L-Homoprolin-1-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]benzylamid-Hydrochlorid

L-Homoprolin-1-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]adamant-1-ylmethylamid-Hydrochlorid

L-Homoprolin-1-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]tetrahydrofurfurylamid

L-Homoprolin-1-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-2-(4-sulfamoylphenyl)ethylamid

L-Homoprolin-1-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-(S)-α-methylbenzylamid-Hydrochlorid

L-Homoprolin-1-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-(1-(S)-[2'-(S)-methylpropyl]3-phenylprop-2-E-enyl) amid

L-Homoprolin-1-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-(1-(S)-[2'-(S)-methylpropy]-3-phenylpropyl)amid

L-Isoleucin-N-[1-(2-(3,4,5-trimethoxyphenyl)-2-oxoethyl)-L-homoprolyl]benzylamid

L-Prolin-1-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-2-(4-(N-acetyl)aminophenyl)ethylamid

L-Prolin-1-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-2-(4-(N-benzoyl)aminophenyl)ethylamid

L-Prolin-1-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-2-(4-(N-carboalloxy)aminophenyl)ethylamid

L-Prolin-1-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-2-(4-(N-carbobenzyloxy)aminophenyl)ethylamid

L-Homoprolin-1-[2-(3,4,5-trimethoxyphenyl)-2-oxoethyl]-3-(4-(N-carboallyloxy)aminophenyl)propylester-Hydrochlorid

L-Prolin-1-[2-adamantan-1-yl-2-oxoethyl]-3-(4-(N-carboallyloxy)aminophenyl)propylester-Hydrochlorid sowie

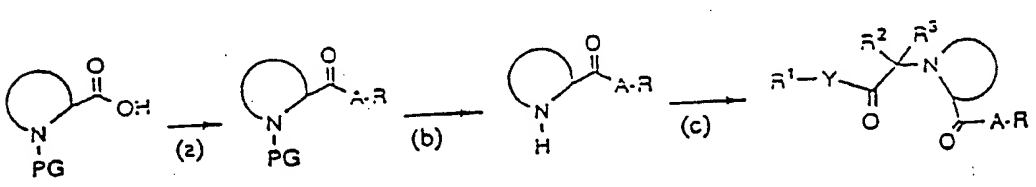
L-Homoprolin-1-[2-adamant-1-yl-2-oxoethyl]-3-(4-(N-carboallyloxy)aminophenyl)propylester-Hydrochlorid.

5. Verbindung gemäß einem der Ansprüche 1 bis 4 zur Behandlung von Entzündungen.

6. Medikament, enthaltend mindestens eine Verbindung gemäß einem der Ansprüche 1 bis 4.

7. Verwendung der verbindungen gemäß einem der Ansprüche 1 bis 4, zur Herstellung einer Zusammensetzung zur Behandlung von Entzündungen.

8. Verfahren zur Herstellung von Verbindungen von einem der Ansprüche 1 bis 4, welches die folgenden Stufen umfaßt:



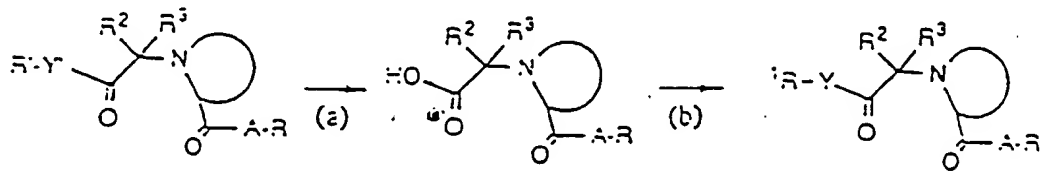
in denen man

(a) eine N-geschützte Iminosäure an ein Amin oder einen Alkohol kuppelt, um eine C-substituierte, N-geschützte Iminosäure zu bilden,

(b) die Schutzgruppe aus der genannten C-substituierten, N-geschützten Iminosäure abspaltet, und

(c) die aus Stufe (b) entstandene Iminosäure an der Stickstoff-Position mit einem α-Haloester, α-Haloketon oder einem α-Haloamid alkyliert.

9. Verfahren zur Herstellung von Verbindungen gemäß einem der Ansprüche 1 bis 4, welches die folgenden Stufen umfaßt:

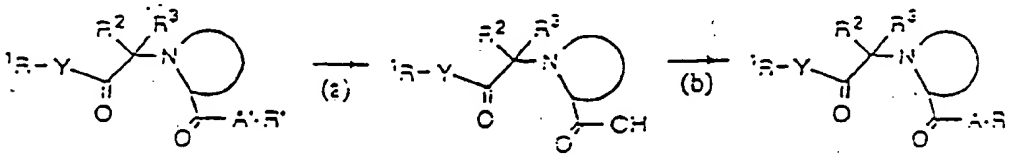


in denen man

(a) aus der 2-Position eines ersten 2-Oxoethyl-Derivats die Schutzgruppe abspaltet und

(b) das aus Stufe (a) entstandene Säure-Derivat zur Bildung eines zweiten 2-Oxoethyl-Derivats einer Kupplungsreaktion unterzieht.

10. Verfahren zur Herstellung von vebindungen gemäß einem der Ansprüche 1 bis 4, welches die folgenden Stufen umfaßt:



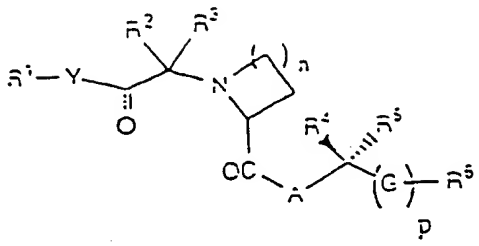
in denen man

(a) aus den C-Enden der Iminosäure eines 2-Oxoethyl-Derivats zur Bildung einer 2-Oxoethyliminosäure die Schutzgruppe abspaltet und

(b) die genannte aus Stufe (a) entstandene 2-Oxoethyliminosäure mit einem Amin oder einem Alkohol kuppelt, um ein C-substituiertes 2-Oxoethyliminosäure-Derivat zu bilden.

Revendications

1. Composé de structure suivante :



(I)

dans laquelle

R^1 représente

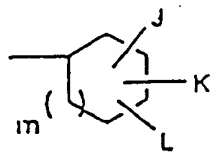
a) l'hydrogène,
b) un groupe alkyle linéaire ou ramifié en C_1 à C_8 qui peut être substitué indépendamment ou simultanément jusqu'à deux fois par

i) un groupe hydroxy,
ii) un groupe phényle qui peut être substitué par un radical alkyle normal ou ramifié en C_1 à C_8 ou un radical alkoxy normal ou ramifié en C_1 à C_6,
iii) un groupe cycloalkyle en C_3 à C_{10} qui peut être substitué par un radical alkyle normal ou ramifié en C_1 à C_8 ou un radical alkoxy normal ou ramifié en C_1 à C_6,
iv) un groupe bicycloalkyle en C_6 à C_{12} qui peut être substitué par un radical alkyle normal ou ramifié en C_1 à C_{10} ou un radical alkoxy normal ou ramifié en C_1 à C_6,
v) un groupe tricycloalkyle en C_7 à C_{14} qui peut être substitué par un radical alkyle normal ou ramifié en C_1 à C_8 ou un radical alkoxy normal ou ramifié en C_1 à C_6,
vi) un groupe tétracycloalkyle en C_{10} à C_{14} qui peut être substitué par un radical alkyle normal ou ramifié en C_1 à C_8 ou un radical alkoxy normal ou ramifié en C_1 à C_6, ou
vii) un groupe morpholinyle,

c) un alcène en C_3 à C_{10}, un diène en C_4 à C_{10} ou un triène en C_8 à C_{18}, qui peut être substitué indépendamment ou simultanément jusqu'à trois fois par

i) un groupe phényle,
ii) un groupe alkyle normal ou ramifié en C_1 à C_6 ou
iii) un groupe alkoxy normal ou ramifié en C_1 à C_6,

d) un groupe cycloalkyle en C_5 à C_{10}, ou le fragment cycloalkyle



dans lequel

m est un nombre entier égal à 0, 1 ou 2,
J, K et L représentent indépendamment ou simultanément

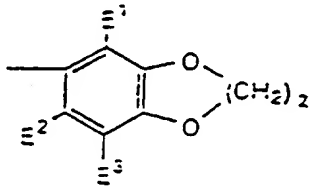
i) de l'hydrogèn
ii) un groupe alkyle normal ou ramifié en C_1 à C_5 qui peut être substitué par un radical

phényle ou par un radical alkoxy normal ou ramifié en C_1 à C_6,
iii) un groupe alkoxy normal ou ramifié en C_1 à C_5,
iv) un groupe phényle ou
v) un groupe phényle substitué par un radical alkyle normal ou ramifié en C_1 à C_6 ou par du chlore ou un radical alkoxy normal ou ramifié en C_1 à C_6,

e) un groupe bicycloalkyle en C_7 à C_{10}, tricycloalkyle en C_7 à C_{14}, tétracycloalkyle en C_{10} à C_{16} ou pentacycloalkyle en C_{11} à C_{20}, qui peut être substitué indépendamment ou simultanément jusqu'à trois fois avec un radical alkyle normal ou ramifié en C_1 à C_6 ou un radical alkoxy normal ou ramifié en C_1 à C_6 ou phényle,
f) les dérivés aryliques tétrahydronaphtyle, benzothiényle, benzofuryle, benzopyrannyle, furyle, pyridyle, pyrannyle, 1,3-oxazolyle ou naphtyle, ces dérivés aryliques pouvant être substitués indépendamment ou simultanément jusqu'à deux fois par

i) un groupe alkyle normal ou ramifié en C_1 à C_6,
ii) un groupe alkoxy normal ou ramifié en C_1 à C_6,
iii) un halogène, cet halogène étant un radical fluoro, chloro, bromo ou iodo,

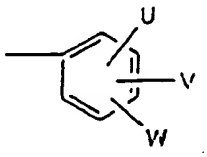
g) le fragment pipéronyle



dans lequel

z est le nombre entier 1 ou 2,
et E^1, E^2 et E^3 peuvent représenter indépendamment ou simultanément de l'hydrogène, un groupe alkyle normal ou ramifié en C_1 à C_6, alkoxy normal ou ramifié en C_1 à C_6 ou du chlore, ou

h) le dérivé arylique



dans lequel

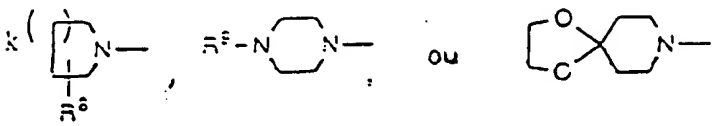
U, V et W peuvent représenter indépendamment ou simultanément

i) l'hydrogène,
ii) un groupe alkyle normal ou ramifié en C_1 à C_6, un groupe alkoxy normal ou ramifié en C_1 à C_6, un groupe phényle ou phénoxy, ces groupes pouvant être substitués par un radical phényle, alkoxy normal ou ramifié en C_1 à C_6 ou phénoxy,
iii) un groupe hydroxy,
iv) un halogène,
v) un groupe nitro ou
vi) un groupe benzoyle ;

Y est une liaison covalente, de l'oxygène, un groupe NR^7 dans lequel R^7 est de l'hydrogène,

en outre,

R^1- Y - peut aussi représenter un groupe



dans lequel

k est le nombre entier 1 ou 2,

R^8 représente

a) de l'hydrogène,
b) un groupe carbalkoxy avec un alkoxy normal ou ramifié en C_1 à C_6,
c) un groupe alkyle normal ou ramifié en C_1 à C_6 qui peut être substitué par un radical phényle ou un radical alkoxy normal ou ramifié en C_1 à C_6,
d) un groupe phényle, ou phényle substitué par un halogène,

R^9 est un groupe phényle qui peut être substitué par un radical alkyle normal ou ramifié en C_1 à C_6 ;

R^2 et R^3 sont définis comme suit : l'un de R^2 et R^3 est de l'hydrogène et l'autre est de l'hydrogène ou un radical alkyle normal ou ramifié en C_1 à C_6 ;

n est le nombre entier 2 ou 3 ;

A est un groupe NR^{10} dans lequel R^{10} est de l'hydrogène ou un radical alkyle normal ou ramifié en C_1 à C_6 ;

R^4 et R^5 peuvent représenter indépendamment ou simultanément

a) de l'hydrogène,
b) un groupe alkyle normal ou ramifié en C_1 à C_8 qui peut être substitué par

i) un groupe phényle ou phényle substitué par un radical hydroxy ou alkoxy en C_1 ou C_2,
ii) un groupe cycloalkyle en C_5 ou C_6,
iii) un groupe alkylthio en C_1 à C_6,
iv) un groupe carboxamido,
v) un groupe alkoxy normal ou ramifié en C_1 à C_6 qui peut être substitué par un radical phényle,

c) un groupe phényle ou
d) un groupe cycloalkyle en C_3 à C_7 qui peut être substitué par un radical alkyle normal ou ramifié en C_1 à C_6, en outre, R^4 et R^5, pris conjointement, peuvent représenter un groupe

$$-(CH_2)_r-$$

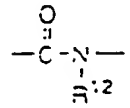
dans lequel

r est le nombre entier 4 ou 5 ;

G est l'un des fragments suivants :

$$-HC=CH-,\ -CH_2\cdot CH_2-,\ \text{ou}\ -CH_2-$$

ou le fragment suivant



dans lequel R^{12} est de l'hydrogène ou un groupe méthyle, de telle sorte que le groupe carbonyle soit attaché à l'atome de carbone portant R^4 et R^5 et que NR^{12} soit lié à R^6 ;

p est le nombre entier 0 ou 1 ;
R^6 représente

a) de l'hydrogène,
b) un groupe alkyle normal ou ramifié en C_1 à C_6 qui peut être substitué par

i) un groupe phényle,
ii) un groupe phényle substitué par un radical alkyle normal ou ramifié en C_1 à à C_6, un radical alkoxy normal ou ramifié en C_1 à C_6, ou
iii) un groupe pyridyle, ou

c) un groupe phényle, naphtyle, furyle, thiofuryle, cycloalkyle en C_5 à C_6, bicycloalkyle en C_6 à C_{10}, tricycloalkyle en C_7 à C_{12}, tétracycloalkyle en C_{10} à C_{16}, pentacycloalkyle en C_{11} à C_{20} ou benzoyle, ces groupes pouvant être substitués par

i) une amine,
ii) un groupe amino substitué par un radical alkoxycarbonyle normal ou ramifié à reste alkoxy en C_1 à C_6, qui peut être substitué par un radical phényle ou un alcène en C_2 à C_6,
iii) un groupe amino substitué par un radical alcanoyle en C_1 à C_6 ou benzoyle,
iv) un groupe sulfonamide ($-SO_2NH_2$) ou
v) un groupe hydroxy ou un groupe alkoxy normal ou ramifié en C_1 à C_6 qui peut être substitué par un radical phényle ;

et ses sels acceptables du point de vue pharmaceutique.

2. Composé de formule (I) suivant la revendication 1, dans laquelle

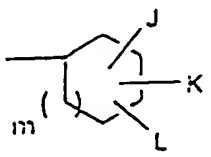
R^1 représente

a) de l'hydrogène,
b) un groupe alkyle linéaire ou ramifié en C_1 à C_6 qui peut être substitué

i) une fois par un groupe hydroxy,
ii) une fois par un groupe phényle qui peut être substitué par un radical alkyle normal ou ramifié en C_1 à C_4 ou par un radical alkoxy normal ou ramifié en C_1 à C_6,
iii) une fois par un groupe cycloalkyle en C_3 à C_8 qui peut être substitué par un radical alkyle normal ou ramifié en C_1 à C_6 ou par un radical alkoxy normal ou ramifié en C_1 à C_4,
iv) une fois par un groupe bicycloalkyle en C_6 à C_{10} qui peut être substitué par un radical alkyle normal ou ramifié en C_1 à C_8 ou par un radical alkoxy normal ou ramifié en C_1 à C_4,
v) une fois par un groupe tricycloalkyle en C_7 à C_{12} qui peut être substitué par un radical alkyle normal ou ramifié en C_1 à C_6 ou par un radical alkoxy normal ou ramifié en C_1 à C_4,
vi) une fois par un groupe tétracycloalkyle en C_{10} à C_{12} qui peut être substitué par un radical alkyle normal ou ramifié en C_1 à C_8 ou par un radical alkoxy normal ou ramifié en C_1 à C_4,
vii) jusqu'à deux fois par un groupe phényle ou cycloalkyle en C_5 à C_7, ou
viii) jusqu'à deux fois par un groupe phényle ou morpholinyle,

c) un alcène en C_3 à C_8 qui peut être substitué par un radical phényle, alkyle normal ou ramifié en C_1 à C_4 ou alkoxy normal ou ramifié en C_1 à C_4.

d) un diène en C_4 à C_7 substitué par un radical alkyle normal ou ramifié en C_1 à C_6, ou par un radical alkoxy normal ou ramifié en C_1 à C_4,
e) un triène en C_{10} à C_{16} substitué jusqu'à trois fois par un radical alkyle normal ou ramifié en C_1 à C_6 ou par un radical alkoxy normal ou ramifié en C_1 à C_4, ou
f) un groupe cycloalkyle en C_5 à C_{10} ou le fragment cycloalkyle



dans lequel

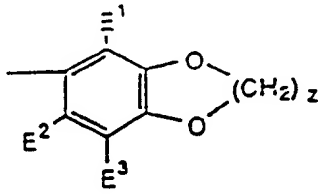
m est le nombre entier 0, 1 ou 2,
J, K et L représentent indépendamment ou simultanément

i) de l'hydrogène,
ii) un groupe alkyle normal ou ramifié en C_1 à C_5 qui peut être substitué par un radical phényle ou un radical alkoxy normal ou ramifié en C_1 à C_4,
iii) un groupe phényle ou
iv) un groupe phényle substitué par un radical alkyle normal ou ramifié en C_1 à C_4 ou par du chlore ou un radical alkoxy normal ou ramifié en C_1 à C_4,

g) un groupe bicycloalkyle en C_7 à C_{10} qui peut être substitué jusqu'à trois fois avec un radical alkyle normal ou ramifié en C_1 à C_6 ou un radical alkoxy normal ou ramifié en C_1 à C_4,
h) un groupe tricycloalkyle en C_7 à C_{14} qui peut être substitué jusqu'à trois fois avec un radical alkyle normal ou ramifié en C_1 à C_6 ou un radical alkoxy normal ou ramifié en C_1 à C_4,
i) un groupe tétracycloalkyle en C_{10} à C_{15} qui peut être substitué jusqu'à trois fois par un radical alkyle normal ou ramifié en C_1 à C_6 ou par un radical alkoxy normal ou ramifié en C_1 à C_4,
j) des dérivés naphtyle ou les dérivés hétéroaryliques benzothiényle, benzofuryle, benzopyrannyle, furyle, pyridyle, pyrannyle ou 1,3-oxazolyle, ces dérivés pouvant être substitués jusqu'à deux fois par

i) un groupe alkyle normal ou ramifié en C_1 à C_6,
ii) un halogène,
iii) ou les deux,

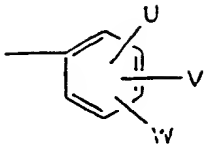
k) un groupe 1,2,3,4-tétrahydronaphtyle,
l) le fragment pipéronyle



dans lequel

z est le nombre entier 1 ou 2,
et E^1, E^2 et E^3 peuvent représenter, indépendamment ou simultanément, l'hydrogène, un groupe alkyle normal ou ramifié en C_1 à C_4, un groupe alkoxy normal ou ramifié en C_1 à C_4 ou du chlore,

m) le dérivé arylique



où

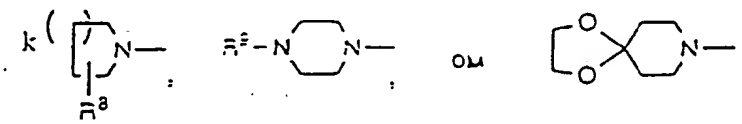
U, V et W peuvent représenter indépendamment ou simultanément

i) de l'hydrogène,
ii) un groupe alkyle normal ou ramifié en C_1 à C_4 qui peut être substitué par un radical phényle,
iii) un groupe alkoxy normal ou ramifié en C_1 à C_6 qui peut être substitué par un radical phényle, un radical alkoxy normal ou ramifié en C_1 à C_4 ou un radical phénoxy,
iv) un groupe hydroxy,
v) un groupe phényle,
vi) un halogène,
vii) un groupe nitro,
viii) un groupe benzoyle ou
ix) un groupe phénoxy ;

Y est une liaison covalente, de l'oxygène, un groupe NR^7, dans lequel R^7 est de l'hydrogène,

en outre

R^1 - Y - peut aussi représenter un groupe



dans lequel

k est le nombre entier 1 ou 2,
R^8 représente

a) de l'hydrogène
b) un groupe carbalkoxy ayant une partie alkoxy normale ou ramifiée en C_1 à C_4,
c) un groupe alkyle normal ou ramifié en C_1 à C_4 qui peut être substitué par un radical phényle ou par un radical alkoxy normal ou ramifié en C_1 à C_4, ou bien
d) est un groupe phényle ou un groupe phényle substitué par un halogène,

R^9 est un groupe phényle qui peut être substitué par un radical alkyle en C_1 à C_4 ;

R^2 et R^3 ont la définition suivante : l'un de R^2 et R^3 est de l'hydrogène et l'autre est de l'hydrogène ou un groupe alkyle normal ou ramifié en C_1 à C_6 ;
n est un nombre entier de 2 ou 3 ;
A est un groupe NR^{10}, dans lequel R^{10} est de l'hydrogène ou un radical alkyle normal ou ramifié en C_1 à C_4.

R^4 est

a) de l'hydrogène,
b) un groupe alkyle normal ou ramifié en C_1 à C_6 qui peut être substitué par

i) un radical phényle ou phényle substitué par un radical hydroxy ou méthoxy,
ii) un groupe cycloalkyle en C_5 ou C_6,
iii) un groupe alkylthio en C_1 à C_6,
iv) un groupe carboxamido ou
v) un groupe alkoxy normal ou ramifié en C_1 à C_6 qui peut être substitué par un radical phényle,

c) un groupe phényle, ou
d) un groupe cycloalkyle en C_3 à C_7 qui peut être substitué par un radical alkyle normal ou ramifié en C_1 à C_6,

R^5 est de l'hydrogène ou un groupe alkyle normal ou ramifié en C_1 à C_4, et R^4 et R^5, considérés ensemble, peuvent représenter un groupe

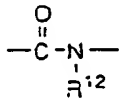
$$-(CH_2)_r-$$

dans lequel

r est le nombre entier 4 ou 5 ;
G est l'un des fragments suivants :

$$-HC{=}CH-,\ -CH_2{\cdot}CH_2-,\ \text{ou}\ -CH_2-$$

ou le fragment suivant



dans lequel le groupe carbonyle est lié à l'atome de carbone portant R^4 et R^5 et NR^{12} est lié à R^6,

R^{12} est de l'hydrogène ou un groupe méthyle ;
P est le nombre entier 0 ou 1 ;
R^6 représente

a) de l'hydrogène,
b) un groupe alkyle normal ou ramifié en C_1 à C_4 qui peut être substitué par

i) un groupe phényle,
ii) un groupe phényle substitué par un radical alkyle normal ou ramifié en C_1 à C_4 ou alkoxy normal ou ramifié en C_1 à C_4, ou bien
iii) un groupe 2- ou 4-pyridyle,

c) un groupe phényle ou naphtyle qui peut être substitué par

i) une amine,
ii) un groupe amino substitué avec un radical alkoxycarbonyle normal ou ramifié à reste alkoxy en C_1 à C_6, qui peut être substitué par un radical phé-

nyle ou un alcène en C_2 à C_6,
iii) un groupe amino substitué par un radical alcanoyle en C_1 à C_6 ou un radical benzoyle,
iv) un groupe sulfonamide ($-SO_2NH_2$) ou
v) un groupe alkoxy normal ou ramifié en C_1 à C_6 qui peut être substitué par un radical phényle,

d) un groupe benzoyle,
e) un groupe furyle ou thiofuryle ou
f) un groupe cycloalkyle en C_5 à C_8, bicycloalkyle en C_6 à C_{10}, tricycloalkyle en C_7 à C_{12} ou tétracycloalkyle en C_{10} à C_{14} ;

et les sels pharmaceutiquement acceptables de ce composé.

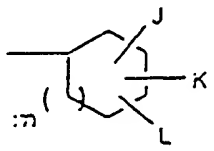
3. Composé de formule (I) suivant la revendication 1, dans lequel

R^1 représente

a) l'hydrogène,
b) un groupe alkyle linéaire ou ramifié en C_1 à C_6 qui peut être substitué par

i) un groupe hydroxy,
ii) un groupe phényle ou un groupe phényle substitué par un radical alkyle normal ou ramifié en C_1 à C_4,
iii) un groupe cycloalkyle en C_3 à C_8 qui peut être substitué par un radical alkyle normal ou ramifié en C_1 à C_4,
iv) un groupe bicycloalkyle en C_6 à C_9 qui peut être substitué par un radical alkyle normal ou ramifié en C_1 à C_6,
v) un groupe tricycloalkyle en C_7 à C_{12} qui peut être substitué par un radical alkyle normal ou ramifié en C_1 à C_4,
vi) un groupe tétracycloalkyle en C_{10} à C_{12} qui peut être substitué par un radical alkyle normal ou ramifié en C_1 à C_6,
vii) un groupe phényle ainsi qu'un groupe cycloalkyle en C_5 ou C_6, ou
viii) un groupe phényle ainsi qu'un groupe morpholinyle,

c) un alcène en C_3 à C_6 qui peut être substitué par un radical phényle,
d) un diène en C_5 ou C_6 substitué par un radical alkyle normal ou ramifié en C_1 à C_4,
e) un triène en C_{13} à C_{16} substitué jusqu'à trois fois par un radical alkyle normal ou ramifié en C_1 à C_4,
f) un groupe cycloalkyle en C_5 ou C_6, ou le fragment cycloalkyle



dans lequel

m est le nombre entier 0, 1 ou 2,
J, K et L représentent indépendamment ou simultanément

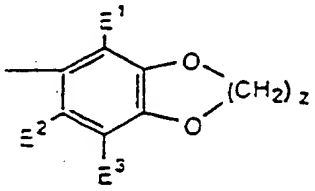
i) de l'hydrogène,
ii) un groupe alkyle n rmal ou ramifié n C_1 à C_5,
iii) un group phényle u
iv) un groupe phényle substitué par un radical alkyle normal ou ramifié en C_1 à C_4, ou

du chlore ou un radical alkoxy normal ou ramifié en C_1 à C_4,

g) un groupe bicycloalkyle en C_7 ou C_8 qui peut être substitué jusqu'à trois fois avec un radical alkyle normal ou ramifié en C_1 à C_4,
h) un groupe tricycloalkyle en C_7 à C_{12} qui peut être substitué jusqu'à deux fois avec un radical alkyle normal ou ramifié en C_1 à C_6,
i) un groupe tétracycloalkyle en C_{10} à C_{12} qui peut être substitué jusqu'à trois fois par un radical alkyle normal ou ramifié en C_1 à C_4,
j) un groupe 2-benzothiényle substitué indépendamment ou simultanément au moins deux fois par

i) un groupe alkyle normal ou ramifié en C_1 à C_3,
ii) du chlore
iii) ou les deux,

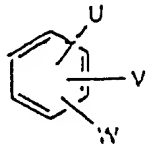
k) un groupe furyle,
l) un groupe 2-pyridyle,
m) un groupe 2-naphtyle,
n) un groupe 1,2,3,4-tétrahydronaphtyle,
o) un groupe 2-benzopyrannyle,
p) un groupe 2-benzofuryle,
q) le fragment pipéronyle



dans lequel

z est le nombre entier 1 ou 2,
et E^1, E^2 et E^3 représentent de l'hydrogène, ou bien

r) le dérivé arylique



dans lequel

U, V et W peuvent représenter, indépendamment ou simultanément

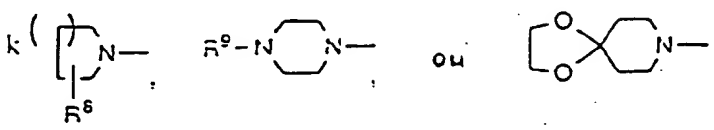
i) de l'hydrogène
ii) un groupe alkyle normal ou ramifié en C_1 à C_4,
iii) un groupe alkoxy normal ou ramifié en C_1 à C_4,
iv) un groupe alkoxy en C_2 substitué par un radical alkoxy en C_2 ou phénoxy,
v) un groupe hydroxy,
vi) un groupe phényle,

vii) du fluor,
viii) du chlore,
ix) du brome,
x) un groupe nitro,
xi) un groupe benzyloxy,
xii) un groupe benzoyle,
xiii) un groupe phénoxy ;

Y est une liaison covalente, de l'oxygène, un groupe NR^7 dans lequel R^7 est de l'hydrogène ;

en outre,

R^1-Y- peut aussi représenter un groupe



dans lequel

k est le nombre entier 1 ou 2,
R^8 représente

a) de l'hydrogène,
b) un groupe carbalkoxy dont la partie alkoxy est en C_1 ou C_2,
c) un groupe alkyle normal ou ramifié en C_1 à C_4 qui peut être substitué par un radical phényle,
d) un groupe phényle,

R^9 est un groupe phényle ;
R^2 et R^3 sont définis comme suit : l'un de R^2 et R^3 est de l'hydrogène et l'autre est de l'hydrogène ou un groupe alkyle normal ou ramifié en C_1 à C_4,
n est le nombre entier 2 ou 3 ;
A est un groupe NR^{10}, dans lequel R^{10} est de l'hydrogène ou un groupe méthyle ;
R^4 représente

a) de l'hydrogène,
b) un groupe alkyle normal ou ramifié en C_1 à C_4 qui peut être substitué par

i) un groupe phényle,

ii) un groupe cycloalkyle en C_5 ou C_6,

iii) un groupe alkylthio en C_1 à C_4,

iv) un groupe carboxamido, ou

v) un groupe benzyloxy, ou bien

c) un groupe phényle ;

R^5 est de l'hydrogène ou un groupe alkyle normal ou ramifié en C_1 à C_4, et R^4 et R^5, considérés ensemble, peuvent représenter un groupe

$-(CH_2)_r-$

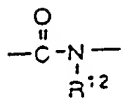
dans lequel

r est le nombre entier 5 ;

G est l'un des fragments suivants :

$-HC=CH-$, $-CH_2\cdot CH_2-$, ou $-CH_2-$

ou le fragment suivant :



dans lequel le groupe carbonyle est lié à l'atome de carbone portant R^4 et R^5 et NR^{12} est lié à R^6,

R^{12} est de l'hydrogène ou un groupe méthyle ;
p est le nombre entier 0 ou 1 ;
R^6 représente

a) de l'hydrogène,
b) un groupe alkyle normal ou ramifié en C_1 à C_4 qui peut être substitué par

i) un groupe phényle,
ii) un groupe phényle substitué par un radical alkoxy en C_1 ou C_2,
iii) un groupe 2- ou 4-pyridyle,

c) un groupe phényle qui peut être substitué par

i) un groupe amino,
ii) un groupe amino substitué par un radical allyloxycarbonyle,
iii) un groupe amino substitué par un radical acétyle,
iv) un groupe amino substitué par un radical benzoyle,
v) un groupe amino substitué par un radical benzyloxycarbonyle,
iii) un groupe sulfonamide ($-SO_2NH_2$), ou
iv) un groupe alkoxy normal ou ramifié en C_1 à C_4,

d) un groupe benzoyle,
e) un groupe furyle,
f) un groupe naphtyle,
g) un groupe cycloalkyle en C_5 à C_8, ou
h) un groupe tétracycloalkyle en C_{10} à C_{12} ;

et les sels pharmaceutiquement acceptables de ce composé.

4. Composé suivant les revendications 1 à 3, choisi dans le groupe consistant en :

N-[1-(2-benzyloxy-2-oxoéthyl)-L-prolyl]benzylamidede L-isoleucine ;
N-[1-(2-méthoxy-2-oxoéthyl)-L-prolyl]benzylamide d L-isoleucine ;
N-[1-(2-phényl-2-oxoéthyl)-L-prolyl]b nzylamide d L-isoleucine ;
N-[1-(2-napht-2-yl-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;

N-[1-(2-(biphényl-4-yl)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(2-méthoxyphényl)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucin ;
N-[1-(2-(5-chloro-3-méthylbenzo[B]thiophène-2-yl)-2-oxo-éthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-trans,trans-hexa-2,4-diényl-1-oxy)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(4-chlorophényl)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(4-méthylphényl)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(4-méthoxyphényl)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-méthyl-N-[1-(2-phényl-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-phényl-2-oxoéthyl)-L-homoproline]benzylamide de L-isoleucine ;
N-[1-(2-phényl-2-oxoéthyl)-L-proline-benzylamide de L-phénylglycine ;
N-[1-(1-méthyl-2-phényl-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(3-méthoxyphényl)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(3,4-dihydroxyphényl)-2-oxoéthyl)-L-prolyl]benzyl-amide de L-isoleucine ;
N-méthyl-N-[1-(2-benzyloxy-2-oxoéthyl)-L-prolyl] benzylamide de L-isoleucine ;
N-[1-(carbobenzyloxyméthylène)-L-homoproline-benzylamide de L-isoleucine ;
N-[1-(2-adamantan-1-yl-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(carbo-tertio-butoxyméthylène)-L-proline]benzylamide de L-isoleucine ;
N-[1-(2-tertio-butyl-2-oxoéthyl)-L-proline]benzylamide de L-isoleucine ;
N-[1-(2-(2,5-diméthoxyphényl)-2-oxoéthyl)-L-prolyl]benzyl-amide de L-isoleucine ;
N-[1-(2-(2,4-diméthoxyphényl)-2-oxoéthyl)-L-prolyl]benzyl-amide de L-isoleucine ;
N-[1-(2-(2-nitrophényl)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(4-nitrophényl)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(3-benzyloxyphényl)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(2,4-diméthylphényl)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(4-fluorophényl)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(4-bromophényl)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2,4-dichlorophénylcarbamoylméthyl)-L-proline]benzyl-amide de L-isoleucine ;
N-[1-(2-adamantan-1-yl-2-oxoéthyl)-L-homoproline]benzylamide de L-isoleucine ;
N-[1-(2-furanne-2-yl-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-pyrid-2-yl-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(adamant-1-ylcarbamoylméthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(cis-octahydro-pentalène-1-yl)-2-oxoéthyl)-L-prolyl]-benzylamide de L-isoleucine ;
N-[1-[2-(2,6,6-triméthyl-bicyclo[3.1.1]hept-3-yl)-2-oxo-éthyl]-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(4-pentylcyclohexyl)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(1,2,3,4-tétrahydro-naphtalène-2-yl)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(1-méthyl-cyclohexyl)-2-oxoéthyl)-L-prolyl]benzyl-amide de L-isoleucine ;
N-[1-(2-oxo-2-tricyclo[3.3.1.$0^{3,7}$]non-3-yl-éthyl)-L-prolyl]-benzylamide de L-isoleucine ;
N-[1-(2-oxo-3-(3-méthyl-adamantan-1-yl)-propyl)-L-prolyl]-benzylamide de L-isoleucine ;
ester de 1-(2-adamantan-1-yl-2-oxoéthyl)benzyle de L-proline ;
N-[1-(2-(biphényl-4-yl)-2-oxoéthyl)-L-prolyl]1,2,3,4-tétrahydroisoquinolinamide de L-isoleucine ;
ester de N-[1-(2-(biphényl-4-yl)-2-oxoéthyl)-L-prolyl]benzyle de L-isoleucine ;
N-[1-(2-(biphényl-4-yl)-2-oxoéthyl)-L-prolyl]tertio-butyl-amide de L-isoleucine ;
N-[1-(2-(biphényl-4-yl)-2-oxoéthyl)-L-prolyl]benzylamide de L-phénylalanine ;
N-[1-(2-(biphényl-4-yl)-2-oxoéthyl)-L-prolyl]benzylamide de L-méthionine ;
N-[1-(2-adamantan-1-yl-2-oxoéthyl)-L-prolyl]benzylamide de glycine ;
N-[1-(2-adamantan-1-yl-2-oxoéthyl)-L-prolyl]benzylamide de L-valine ;
N-[1-(2-adamantan-1-yl-2-oxoéthyl)-L-prolyl]benzylamide de L-leucine ;
N-[1-(2-adamantan-1-yl-2-oxoéthyl)-L-prolyl]benzylamide de Lphénylalanine ;
N-[1-(2-adamantan-1-yl-2-oxoéthyl)-L-prolyl]benzylamide de L-norvaline ;
N-[1-(2-adamantan-1-yl-2-oxoéthyl)-L-prolyl]benzylamide de L-norleucine ;
N-[1-(2-adamantan-1-yl-2-oxoéthyl)-L-prolyl]benzylamide de L-asparagine ;
N-[1-(2-adamantan-1-yl-2-oxoéthyl)-L-prolyl]benzylamide d'éther O-benzylique de L-sérine ;
N-[1-(2-adamantan-1-yl-2-oxoéthyl)-L-prolyl]benzylamide de L-β-phénylalanine ;
N-[1-(2-adamantan-1-yl-2-oxoéthyl)-L-prolyl]benzylamide de L-cyclohexylalanine ;
N-[1-(2-adamantan-1-yl-2-oxoéthyl)-L-prolyl]alpha-(S)-méthyl-benzylamide de L-isoleucine ;
N-[1-(2-adamantan-1-yl-2-oxoéthyl)-L-prolyl]alpha-(R)-méthyl-benzylamide de L-isoleucine ;
N-[1-(2-adamantan-1-yl-2-oxoéthyl)-L-prolyl]pyridine-4-yl-méthylamide de L-isol ucin ;
N-[1-(2-adamantan-1-yl-2-oxoéthyl)-L-prolyl]pyridine-2-yl-méthylamid de L-isoleucin ;

N-[1-(2-adamantan-1-yl-2-oxoéthyl)-L-prolyl]-4-méthoxybenzyl-amide de L-isoleucine ;
N-[1-(2-adamantan-1-yl-2-oxoéthyl)-L-prolyl]-2-méthoxybenzyl-amide de L-isoleucine ;
N-[1-(carboxyméthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-[2-[N-(pipéridine-3-carboxylate d'éthyle)]-2-oxoéthyl]-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(1,4-dioxa-8-aza-spiro[4.5]déc-8-yl)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-[2-(N-(4-benzylpipéridiyl))-2-oxoéthyl]-L-prolyl]-benzylamide de L-isoleucine ;
N-[1-[2-(2-méthylpipéridine)-2-oxoéthyl]-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(2-hydroxyéthylamine)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-[2-(4-phénylpipérazine)-2-oxoéthyl]-L-prolyl]benzylamide de L-isoleucine ;
N-[1-[2-(1-pyrrolidine)-2-oxoéthyl]-L-prolyl]benzylamide de L-isoleucine ;
N-[1-[2-(N-cyclopentylamino)-2-oxoéthyl]-L-prolyl]benzylamide de L-isoleucine ;
N-[1-[2-N-(phénylméthylamino))-2-oxoéthyl]-L-prolyl]benzyl-amide de L-isoleucine ;
N-[1-[2-(N-(cyclohexylméthylamino))-2-oxoéthyl]-L-prolyl]-benzylamide de L-isoleucine ;
N-[1-(2-(4-phénylpipéridyl)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-[1-(3,7,11-triméthyldodéca-2,6,10-triène-1-ol)]-2-oxoéthyl)-L-proline]benzylamide de L-isoleucine ;
N-[1-(2-(3-phényl-2-propène-1-oxy)-2-oxoéthyl)-L-prolyl]-benzyl-amide de L-isoleucine ;
N-[1-(2-(3-phényl-3-méthyl-2-propène-1-oxy)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(1-phénylpropoxy)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(1-phényl-1-cyclohexylméthoxy)-2-oxoéthyl)-L-prolyl]-benzylamide de L-isoleucine ;
N-[1-(2-(1-phényl-2-(4-morpholino)éthoxy)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(2-oxy-2-méthyladamant-2-yl)-2-oxoéthyl)-L-prolyl]-benzylamide de L-isoleucine ;
N-[1-(adamantan-2-ylcarbamoylméthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(adamant-1-ylméthylcarbamoylméthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(2-méthyl-1-(S)-phényl-1-propoxy)-2-oxoéthyl-L-proly]-benzylamide de L-isoleucine ;
N-[1-(2-(2-méthyl-1-(R)-phényl-1-propoxy)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(4-tertio-butylcyclohexyl)-2-oxoéthyl)-L-prolyl]-benzylamide de L-isoleucine ;
N-[1-(2-bicyclo[2.2.1]hept-2-yl)-2-oxoéthyl)-L-prolyl]-benzylamide de L-isoleucine ;
N-[1-(2-(3,4,5-triméthoxyphényl)-2-oxoéthyl)-L-prolyl]-benzylamide de L-isoleucine ;
chlorhydrate de N-[1-(2-chroman-2-yl)-2-oxoéthyl)-L-prolyl]-benzylamide de L-isoleucine ;
chlorhydrate de N-[1-(2-benzofuranne-2-yl)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(3-benzoyloxyphényl)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(4-benzoyloxyphényl)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(2-benzoyloxyphényl)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(3-phénoxyphényl)2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(2-phénoxyphényl)2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(3,4,5-triéthoxyhényl)2-oxoéthyl)-L-prolyl]benzyl-amide de L-isoleucine ;
N-(1-(2-benzo[1.3]dioxole]-5-yl)-2-oxoéthyl)-L-prolyl]benzyl-amide de L-isoleucine ;
N-[1-{2-oxo-2-[4-(2-phénoxyéthoxy)-phényl]-éthyl]-L-prolyl]-benzylamide de L-isoleucine ;
N-[1-(2-(4-phénoxyphényl)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(2,4,6-triméthoxyphényl)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(2,3-diméthoxyphényl)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(2,6-diméthoxyphényl)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(1-(4-méthylphényl) cyclohexyl)-2-oxoéthyl)-L-prolyl]-benzylamide de L-isoleucine ;
N-[1-(2-(1-(4-chlorophényl)cyclohexyl)-2-oxoéthyl)-L-prolyl]-benzylamide de L-isoleucine ;
N-[1-(2-(2,3,4-triméthoxyphényl)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(1-phénylcyclohexyl)-2-oxoéthyl)-L-prolyl]benzylamide de L-isoleucine ;
N-[1-(2-(2,4,5-triméthoxyphényl)-2-oxoéthyl)-L-prolyl]benzyl-amide de L-isoleucine ;
chlorhydrate d'ester benzylique de 1-[2-(3,4,5-triméthoxyphényl)-2-oxoéthyl]-L-proline
chlorhydrate de 1-[2-(3,4,5-triméthoxyphényl)-2-oxoéthyl]-benzylamide de L-proline ;
chlorhydrate de 1-[2-(3,4,5-triméthoxyphényl)2-oxoéthyl]-2-phénéthylamide de L-proline ;
chlorhydrate de 1-[2-(3,4,5-triméthoxyphényl)-2-oxoéthyl]-3-phénylpropylamide de L-proline ;
chlorhydrate de 1-[2-(3,4,5-triméthoxyphényl)2-oxoéthyl]-4-phénylbutylamide de L-proline ;
dichlorhydrate de 1-[2-(3,4,5-triméthoxyphényl)2-oxoéthyl]-2-(pyrid-2-yl)éthylamide de L-proline ;
dichlorhydrate de 1-[2-(3,4,5-triméthoxyphényl)-2-oxoéthyl]-2-(4-aminophényl)éthylamide de L-proline ;
chlorhydrate d'ester 1-[2-(3,4,5-triméthoxyphényl)-2-oxo-éthyl]-3-(4-[N-carballyloxy]aminophényl)propylique de L-proline ;
1-[2-(3,4,5-triméthoxyphényl)-2-oxoéthyl]-2-phényl-2-oxoéthylamide de L-proline ;
1-[2-(3,4,5-triméthoxyphényl)-2-oxoéthyl]tétrahydrofurfuryl-amide de L-prolin ;

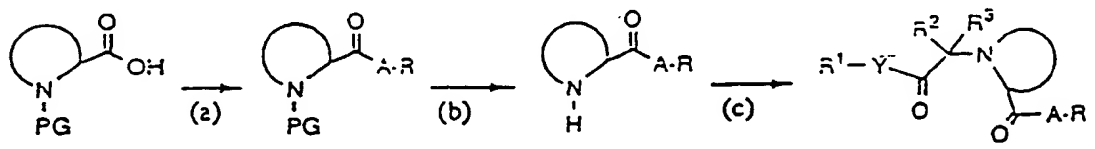
1-[2-(3,4,5-triméthoxyphényl)2-oxoéthyl]naphtal`ne-1-yl-méthylamide d L-pr line ;
1-[2-(3,4,5-triméthoxyphényl)-2-oxoéthyl]2-(4-sulfamoylphényl)éthylamide de L-proline ;
1-[2-(3,4,5-triméthoxyphényl)-2-oxoéthyl]-4-phénylpipéridényl-amide de L-proline ;
chlorhydrate de 1-[2-(3,4,5-triméthoxyphényl)-2-oxoéthyl]-4-méthoxybenzamide de L-proline ;
chlorhydrate de 1-[2-(3,4,5-triméthoxyphényl)-2-oxoéthyl]-3-méthoxybenzamide de L-proline ;
chlorhydrate de 1-[2-(3,4,5-triméthoxyphényl)-2-oxoéthyl]-2-méthoxybenzamide de L-proline ;
chlorhydrate de 1-[2-(3,4,5-triméthoxyphényl)-2-oxoéthyl]-N-méthylphénéthylamide de L-proline ;
chlorhydrate de 1-[2-(3,4,5-triméthoxyphényl)-2-oxoéthyl]-(S)-α-méthylbenzylamide de L-proline ;
chlorhydrate de 1-[2-(3,4,5-triméthoxyphényl)-2-oxoéthyl]-(R)-α-méthylbenzylamide de L-proline ;
chlorhydrate de 1-[2-(3,4,5-triméthoxyphényl)-2-oxoéthyl]-1-méthyl-3-phénylpropylamide de L-proline ;
chlorhydrate de 1-[2-(3,4,5-triméthoxyphényl)2-oxoéthyl]-adamant-1-ylméthylamide de L-proline ;
chlorhydrate de 1-[2-(3,4,5-triméthoxyphényl)-2-oxoéthyl]-1(R)-(1-naphtyl)éthylamide de L-proline ;
1-[2-(3,4,5-triméthoxyphényl)2-oxoéthyl]cyclohexylméthylamide de L-proline ;
chlorhydrate de 1-[2-(3,4,5-triméthoxyphényl)-2-oxoéthyl]di-phénylméthylamide de L-proline ;
chlorhydrate de 1-[2-(3,4,5-triméthoxyphényl)-2-oxoéthyl]-tertio-butylamide de L-proline ;
chlorhydrate de 1-[2-(3,4,5-triméthoxyphényl)-2-oxoéthyl]-1,2-diphényléthylamide de L-proline ;
chlorhydrate de 1-[2-(3,4,5-triméthoxyphényl)2-oxoéthyl]-cyclohexylamide de L-proline ;
chlorhydrate d'ester benzylique de 1-[2-(3,4,5-triméthoxyphényl)-2-oxoéthyl]-L-homoproline
chlorhydrate de 1-[2-(3,4,5-triméthoxyphényl)2-oxoéthyl]-benzylamide de L-homoproline ;
chlorhydrate de 1-[2-(3,4,5-triméthoxyphényl)-2-oxoéthyl]-adamant-1-ylméthylamide de L-homoproline ;
1-[2-(3,4,5-triméthoxyphényl)-2-oxoéthyl]tétrahydrofurfurylamide de L-homoproline ;
1-[2-(3,4,5-triméthoxyphényl)-2-oxoéthyl]-2-(4-sulfamoylphényl)éthylamide de L-homoproline ;
chlorhydrate de 1-[2-(3,4,5-triméthoxyphényl)-2-oxoéthyl]-(S)-α-méthylbenzylamide de L-homoproline ;
1-[2-(3,4,5-triméthoxyphényl)2-oxoéthyl]-(1-(S)-[2'-(S)-méthylpropyl]-3-phénylprop-2-E-ényl)-amide de L-homoproline ;
1-[2-(3,4,5-triméthoxyphényl)2-oxoéthyl]-(1-(S)-[2'-(S)-méthylpropyl]-3-phénylpropyl)-amide de L-homoproline ;
N-[1-(2-(3,4,5-triméthoxyphényl)-2-oxoéthyl)-L-homoprolyl]-benzylamide de L-isoleucine ;
1-[2-(3,4,5-triméthoxyphényl)-2-oxoéthyl]-2-(4-(N-acétyl)-aminophényl)éthylamide de L-proline ;
1-[2-(3,4,5-triméthoxyphényl)-2-oxoéthyl]-2-(4-(N-benzoyl)-aminophényl)éthylamide de L-proline ;
1-[2-(3,4,5-triméthoxyphényl)-2-oxoéthyl]-2-(4-(N-carballoxy)aminophényl)éthylamide de L-proline ;
1-[2-(3,4,5-triméthoxyphényl)2-oxoéthyl]-2-(4-(N-carbobenzyl-oxy)aminophényl)éthylamide de L-proline ;
chlorhydrate d'ester de 1-[2-(3,4,5-triméthoxyphényl)-2-oxoéthyl]-3-(4 (N-carballyloxy)aminophényl)propylique de L-homoproline ;
chlorhydrate d'ester 1-[2-adamantan-1-yl-2-oxoéthyl]-3-(4-(N-carballyloxy)aminophényl)propylique de L-proline ; et
chlorhydrate d'ester 1-[2-adamant-1-yl-2-oxoéthyl]-3-(4-(N-carballyloxy)aminophényl) propylique de L-homoproline.

5. Composé suivant les revendications 1 à 4, destiné au traitement d'inflammations.

6. Médicament contenant au moins un composé suivant les revendications 1 à 4.

7. Utilisation des composés suivant les revendications 1 à 4 pour la préparation d'une composition destinée au traitement d'une inflammation.

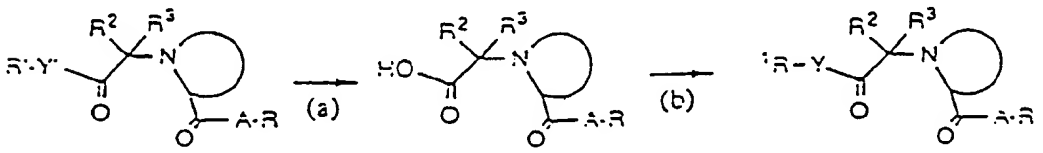
8. Procédé de production de composés suivant les revendications 1 à 4, comprenant les étapes suivantes :



qui sont

(a) le couplage d'un iminoacide protégé sur l'azote à une amine ou à un alcool pour former un iminoacide protégé sur l'azote substitué sur le carbone ;
(b) l'élimination du groupe protecteur de cet iminoacide protégé sur l'azote et substitué sur le carbone : et
(c) l'alkylation de l'iminoacide résultant de l'étape (b) dans la position de l'azote avec un α-halogénester, une α-halogénocétone ou un α-halogénamide.

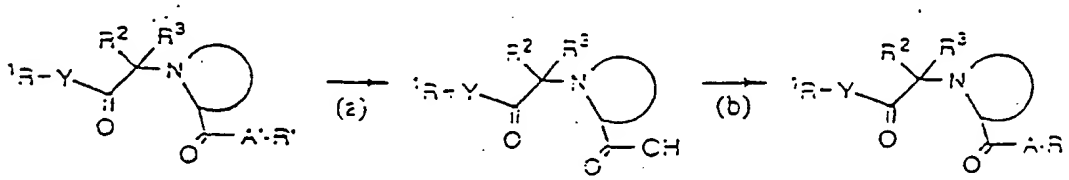
9. Procédé de production des composés suivant les revendications 1 à 4, comprenant les étapes suivantes :



qui sont :

a) l'élimination de la protection en position 2 d'un premier dérivé 2-oxoéthylique ; et
b) le couplage du dérivé acide résultant de l'étape (a) pour former un second dérivé 2-oxoéthylique.

10. Procédé de production des composés suivant les revendications 1 à 4, comprenant les étapes suivantes :



qui sont :

a) l'élimination de la protection des atomes C-terminaux de l'iminoacide d'un dérivé 2-oxoéthylique pour former un iminoacide 2-oxoéthylique ; et
b) le couplage de cet iminoacide 2-oxoéthylique résultant de l'étape (a) à une amine ou un alcool pour former un dérivé d'iminoacide 2-oxoéthylique substitué sur le carbone.